

=> fil reg

FILE 'REGISTRY' ENTERED AT 08:49:32 ON 30 JAN 2004  
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Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 28 JAN 2004 HIGHEST RN 642928-00-5  
DICTIONARY FILE UPDATES: 28 JAN 2004 HIGHEST RN 642928-00-5

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

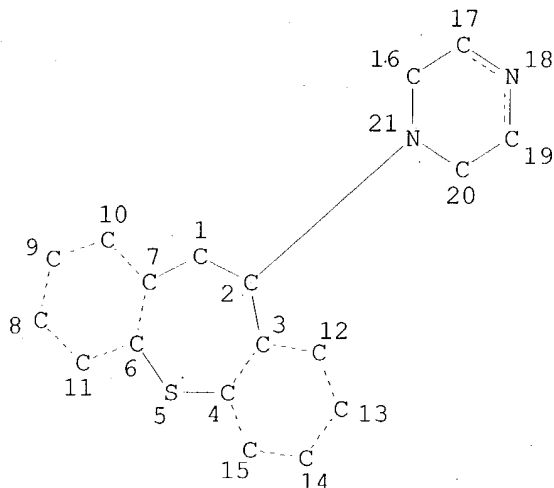
Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more  
information enter HELP PROP at an arrow prompt in the file or refer  
to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d sta que 19

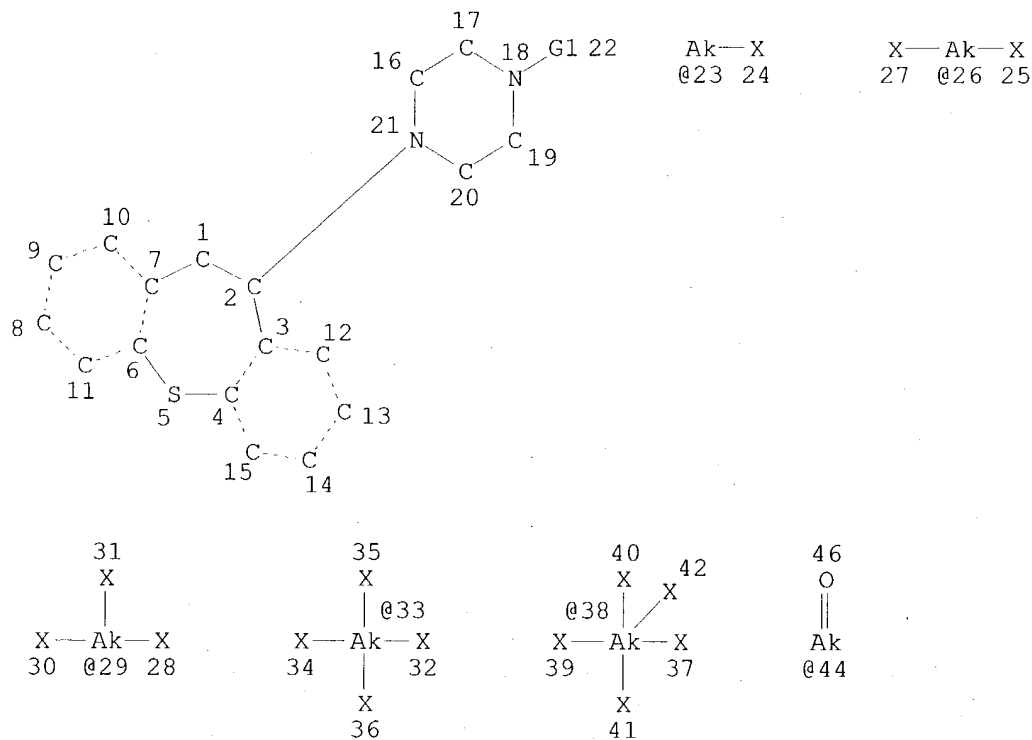
L1 STR



NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE  
L3 1769 SEA FILE=REGISTRY SSS FUL L1  
L4 STR



VAR G1=AK/23/26/29/33/38/44

NODE ATTRIBUTES:

CONNECT IS M1 RC AT 8  
 CONNECT IS M1 RC AT 9  
 CONNECT IS M1 RC AT 10  
 CONNECT IS M1 RC AT 11  
 CONNECT IS M1 RC AT 12  
 CONNECT IS M1 RC AT 13  
 CONNECT IS M1 RC AT 14  
 CONNECT IS M1 RC AT 15  
 CONNECT IS M1 RC AT 38

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 44

STEREO ATTRIBUTES: NONE

L6 561 SEA FILE=REGISTRY SUB=L3 CSS FUL L4

L7 STR

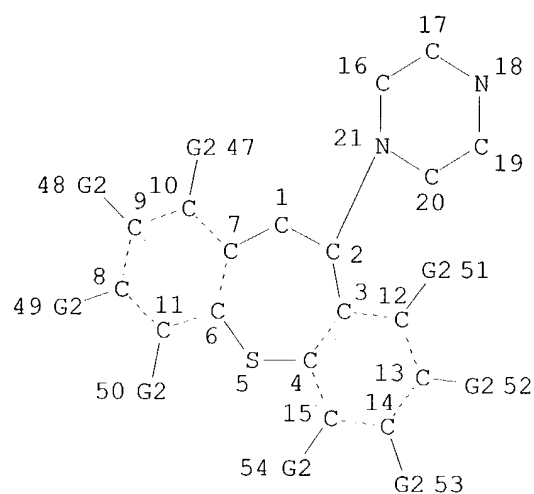
Ak—X  
@23 24

X—Ak—X  
27 @26 25

31  
X  
|  
X—Ak—X  
30 @29 28

46  
O  
||  
Ak  
@44

O—Ak—X  
@57 56 55



N—Ak  
@59 58

62  
Ak  
|  
N—Ak  
@61 60

S—Ak  
@64 63

O—Ak  
@66 65

VAR G2=H/X/AK/66/64/23/26/29/57/NO2/CN/44/NH2/59/61

NODE ATTRIBUTES:

CONNECT IS M1 RC AT 18

CONNECT IS M1 RC AT 29

CONNECT IS M1 RC AT 56

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 52

STEREO ATTRIBUTES: NONE

L9 457 SEA FILE=REGISTRY SUB=L6 CSS FUL L7

100.0% PROCESSED 561 ITERATIONS

SEARCH TIME: 00.00.01

457 ANSWERS

=> d his

(FILE 'HOME' ENTERED AT 08:04:17 ON 30 JAN 2004)  
DEL HIS

FILE 'REGISTRY' ENTERED AT 08:05:18 ON 30 JAN 2004

L1 STR  
L2 50 S L1  
L3 1769 S L1 FUL  
L4 SAV TEMP L3 LE061/A  
L5 STR L1  
L6 25 S L4 CSS SAM SUB=L3  
L7 561 S L4 CSS FUL SUB=L3  
L8 SAV TEMP L6 LE061A/A  
L9 STR L4  
L10 19 S L7 CSS SAM SUB=L6

L9 457 S L7 CSS FUL SUB=L6  
SAV TEMP L9 LE061B/A

FILE 'HCAPLUS' ENTERED AT 08:20:19 ON 30 JAN 2004

L10 618 S L9  
L11 13257 S CMV OR ?CYTOMEGALOVIR?  
E CYTOMEGALOVIR/CT  
E E4+ALL  
L12 2971 S E7  
L13 5744 S E6+NT  
E CYTOMEG/CT  
E E6+ALL  
L14 2 S L10 AND L11-L13  
E SCHALL T/AU  
L15 128 S E3-E10  
E PENFOLD M/AU  
L16 17 S E4-E6  
E CHEMOCENTR/PA,CS  
L17 33 S E5-E14  
E CHEMO CENTR/PA,CS  
L18 2 S L10 AND L15-L17  
L19 1 S US20020182594/PN OR (WO2002-US3229 OR US2001-266094#)/AP,PRN  
L20 3 S L14,L18,L19  
L21 3 S L20 AND L10-L20  
SEL HIT RN

FILE 'REGISTRY' ENTERED AT 08:24:11 ON 30 JAN 2004

L22 4 S E1-E4

FILE 'REGISTRY' ENTERED AT 08:24:33 ON 30 JAN 2004

FILE 'MEDLINE' ENTERED AT 08:24:56 ON 30 JAN 2004

L23 356 S L9  
L24 989 S OCTOCLOTHEPIN? OR CLOTEPIN? OR CLOTHEPIN? OR CLOROTHEPIN? OR  
L25 989 S L23,L24  
L26 28347 S L11  
E CYTOMEGALOVIR/CT  
E E6+ALL  
L27 11117 S E9+NT  
E CYTOMEGALOVIR/CT  
E E9+ALL  
L28 14342 S E5+NT  
E CYTOMEGALOVIR/CT  
E E77+ALL  
L29 22 S E10+NT  
E CYTOMEGALOVIRUS/CT  
E E82+ALL  
L30 1546 S E2+NT  
L31 351 S E4+NT  
L32 0 S L25 AND L26-L31  
E SCHALL T/AU  
L33 89 S E3-E7  
E PENFOLD M/AU  
L34 12 S E3-E5,E8,E9  
L35 0 S L25 AND L33,L34  
L36 10 S L26-L31 AND L33,L34

FILE 'BIOSIS' ENTERED AT 08:31:11 ON 30 JAN 2004

L37 1228 S L25  
L38 31590 S L11  
L39 82214 S HERPESVIRIDAE+NT/BC  
E 02220/BC  
E 02162/BC

E CYTOMEGA/BC  
 E HERP/BC  
 L40 0 S L37 AND L38,L39  
 E SCHALL T/AU  
 L41 146 S E3-E9  
 E PENFOLD M/AU  
 L42 13 S E4-E7  
 L43 0 S L37 AND L41,L42  
 L44 16 S L38,L39 AND L41,L42

FILE 'MEDLINE, BIOSIS' ENTERED AT 08:49:21 ON 30 JAN 2004  
 L45 16 DUP REM L36 L44 (10 DUPLICATES REMOVED)

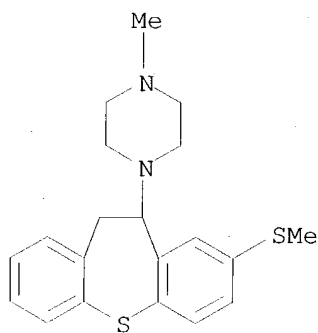
FILE 'REGISTRY' ENTERED AT 08:49:32 ON 30 JAN 2004

=> d ide can tot 122

L22 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN  
 RN 74611-28-2 REGISTRY  
 CN Piperazine, 1-[10,11-dihydro-8-(methylthio)dibenzo[b,f]thiepin-10-yl]-4-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Dibenzo[b,f]thiepin, piperazine deriv.  
 MF C20 H24 N2 S2 . C H4 O3 S  
 LC STN Files: BEILSTEIN\*, CA, CAPLUS, USPATFULL  
 (\*File contains numerically searchable property data)

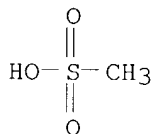
CM 1

CRN 20229-30-5  
 CMF C20 H24 N2 S2



CM 2

CRN 75-75-2  
 CMF C H4 O3 S



4 REFERENCES IN FILE CA (1907 TO DATE)  
 4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:350028

REFERENCE 2: 136:210544

REFERENCE 3: 110:108076

REFERENCE 4: 93:95239

L22 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN

RN 20229-30-5 REGISTRY

CN Piperazine, 1-[10,11-dihydro-8-(methylthio)dibenzo[b,f]thiepin-10-yl]-4-methyl- (8CI, 9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Dibenzo[b,f]thiepin, piperazine deriv.

OTHER NAMES:

CN Methiotepin

CN Methiothepin

CN Methiothepine

CN Metitepine

CN Ro 8-6837

DR 101395-30-6

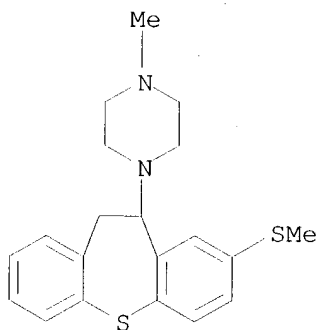
MF C20 H24 N2 S2

CI COM

LC STN Files: AGRICOLA, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK\*, PROMT, RTECS\*, SYNTHLINE, TOXCENTER, USAN, USPATFULL, VETU

(\*File contains numerically searchable property data)

Other Sources: WHO



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

328 REFERENCES IN FILE CA (1907 TO DATE)

3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

328 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:53411

REFERENCE 2: 140:38959

REFERENCE 3: 139:376851

REFERENCE 4: 139:191441

REFERENCE 5: 139:111697

REFERENCE 6: 139:95704

REFERENCE 7: 139:95476

REFERENCE 8: 139:66336

REFERENCE 9: 138:150503

REFERENCE 10: 138:130917

L22 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN

RN 13448-22-1 REGISTRY

CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-  
(8CI, 9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Dibenzo[b,f]thiepin, piperazine deriv.

OTHER NAMES:

CN (±)-Clothepin

CN (±)-Octoclothepin

CN Chlorothepin

CN Clorotepine

CN Clotepin

CN Clothepin

CN Octoclothepin

CN Octoclothepine

DR 41931-02-6

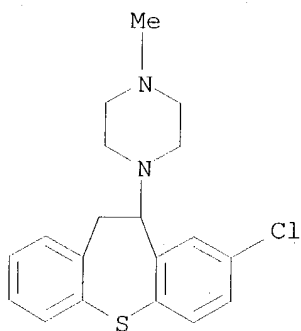
MF C19 H21 Cl N2 S

CI COM

LC STN Files: AGRICOLA, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,  
CAPLUS, CASREACT, DDFU, DRUGU, EMBASE, IPA, MEDLINE, PHAR, PROMT,  
RTECS\*, TOXCENTER, USAN, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: WHO



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

103 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

103 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:62616

REFERENCE 2: 137:103378

REFERENCE 3: 136:226769  
REFERENCE 4: 136:210544  
REFERENCE 5: 136:112520  
REFERENCE 6: 134:126129  
REFERENCE 7: 132:288780  
REFERENCE 8: 128:110756  
REFERENCE 9: 125:50947  
REFERENCE 10: 120:289951

L22 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN

RN 4789-68-8 REGISTRY

CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-,  
(2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Dibenzo[b,f]thiepin, piperazine deriv.

CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-,  
(Z)-2-butenedioate (1:1)

CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-,  
maleate (1:1) (8CI)

OTHER NAMES:

CN OctoclothePIN maleate

FS STEREOSEARCH

DR 41931-03-7

MF C19 H21 Cl N2 S . C4 H4 O4

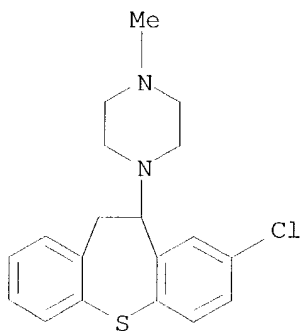
LC STN Files: BEILSTEIN\*, CA, CAOLD, CAPLUS, CHEMCATS, RTECS\*, TOXCENTER,  
USPATFULL

(\*File contains numerically searchable property data)

CM 1

CRN 13448-22-1

CMF C19 H21 Cl N2 S



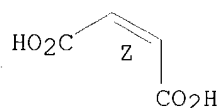
CM 2

CRN 110-16-7

CMF C4 H4 O4

Double bond geometry as shown.





17 REFERENCES IN FILE CA (1907 TO DATE)  
17 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 138:350028  
REFERENCE 2: 136:210544  
REFERENCE 3: 135:335153  
REFERENCE 4: 90:33708  
REFERENCE 5: 89:123059  
REFERENCE 6: 88:182362  
REFERENCE 7: 88:288  
REFERENCE 8: 80:70836  
REFERENCE 9: 80:59966  
REFERENCE 10: 79:92282

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 08:49:55 ON 30 JAN 2004  
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FILE COVERS 1907 - 30 Jan 2004 VOL 140 ISS 6  
FILE LAST UPDATED: 29 Jan 2004 (20040129/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot 121

L21 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN  
AN 2002:615791 HCAPLUS  
DN 137:151988  
ED Entered STN: 16 Aug 2002  
TI Chemomagnetic retrieval of CMV and CMV infected cells

and apparatus

IN Schall, Thomas J.; Penfold, Mark E. T.

PA Chemocentryx, Inc., USA

SO PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N

CC 9-1 (Biochemical Methods)

Section cross-reference(s): 1, 3, 10, 14, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002062956	A2	20020815	WO 2002-US3229	20020201 <--
	WO 2002062956	A3	20030227		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002182594 A1 20021205 US 2002-61944 20020201 <--

PRAI US 2001-266094P P 20010202 <--

OS MARPAT 137:151988

AB Methods and apparatus are provided herein for collecting **CMV** and/or **CMV** infected cells from a host infected with **CMV**. Such methods and apparatus have utility in tracking the dissemination or infection of the host, use as an in vivo or ex vivo collection mechanism to measure mutation rates and selective pressures after in vivo passage, and in therapeutic treatments in which **CMV** and/or **CMV** infected cells are removed from a host.

ST chemomagnetic retrieval **cytomegalovirus** infected cell; app collection **cytomegalovirus** infected cell; **cytomegalovirus** infected cell removal app

IT Proteins

RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)

(US28, apparatus with ligand binding to **cytomegalovirus**; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)

IT Gelatins, biological studies

Polyesters, biological studies

Polyurethanes, biological studies

RL: BUU (Biological use, unclassified); DEV (Device component use); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)

(as absorptive material in implant; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)

IT Particles

(beads, with compound binding to **cytomegalovirus**; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)

IT Magnetic materials

(chemo-; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)

IT Absorbents

Apparatus

Blood

Cell

**Cytomegalovirus**

Mammalia  
 Medical equipment  
 Pumps  
 Sampling apparatus  
 (chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Skin  
 (collection apparatus with patch for application to; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Drug resistance  
 (determination of mutation conferring; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Genetic selection  
 (determination of pressures for; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Mutation  
 (determination of rates of; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Circulation  
 (extracorporeal; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Ligands  
 RL: BUU (Biological use, unclassified); DEV (Device component use); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)  
 (for **cytomegalovirus**; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Prosthetic materials and Prosthetics  
 (implants, with ligand binding to **cytomegalovirus**; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Medical goods  
 (sponges; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Infection  
 (viral; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Colloids  
 Microspheres  
 Nanoparticles  
 (with compound binding to **cytomegalovirus**; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)  
 IT Collecting apparatus  
 (with ligand binding to **cytomegalovirus**; chemomagnetic retrieval of **CMV** and **CMV** infected cells and apparatus)

L21 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2002:172238 HCAPLUS  
 DN 136:226769  
 ED Entered STN: 08 Mar 2002  
 TI US28 and homolog expression by **cytomegaloviruses** and its interaction with chemokines as a basis to prevent **cytomegalovirus** infection and dissemination  
 IN Schall, Thomas J.; Penfold, Mark  
 PA Chemocentryx, Inc., USA  
 SO PCT Int. Appl., 95 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM G01N033-569  
 ICS A61P031-12; A61K039-395; A61K048-00; C07K014-00; C12N015-00; C12N005-00  
 CC 1-5 (Pharmacology)

Section cross-reference(s): 3, 10, 15

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018954	A2	20020307	WO 2001-US27392	20010830
	WO 2002018954	C2	20030327		
	WO 2002018954	A3	20030724		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2001088682	A5	20020313	AU 2001-88682	20010830
	US 2002127544	A1	20020912	US 2001-944163	20010830
	US 2003175681	A1	20030918	US 2001-944049	20010830
	EP 1350113	A2	20031008	EP 2001-968433	20010830
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
PRAI	US 2000-229365P	P	20000830		
	US 2000-228974P	P	20000830		
	US 2000-229191P	P	20000830		
	WO 2001-US27392	W	20010830		
AB	The invention provides methods and compns. for inhibiting <b>cytomegalovirus (CMV)</b> infection and dissemination in an animal, as well as in vitro and in vivo assay systems for identifying such compns. US28 is expressed by human <b>cytomegalovirus</b> as a viorion mol. capable of interacting with fractalkine with high affinity. Rhesus monkey <b>cytomegalovirus</b> expresses at least 5 homologs, with similar chemokine binding activity. <b>CMV</b> dissemination in infected hosts can be inhibited by administration of an inhibitor (e.g., octoclotheptin) of the US28-receptor interaction. Thus, this invention provides screening methods for agents that reduce <b>CMV</b> dissemination in an animal, and treatment of <b>CMV</b> infection.				
ST	US28 homolog gene sequence chemokine interaction <b>cytomegalovirus</b> ; antiviral screening <b>cytomegalovirus</b> US28 chemokine interaction				
IT	Chemokines RL: BSU (Biological study, unclassified); BIOL (Biological study) (C-C; US28 and homolog expression by <b>cytomegaloviruses</b> and its interaction with chemokines as a basis to prevent <b>cytomegalovirus</b> infection and dissemination)				
IT	Chemokines RL: BSU (Biological study, unclassified); BIOL (Biological study) (C-X-C; US28 and homolog expression by <b>cytomegaloviruses</b> and its interaction with chemokines as a basis to prevent <b>cytomegalovirus</b> infection and dissemination)				
IT	Antiviral agents Cercopithecine herpesvirus 8 DNA sequences Drug screening Gene therapy Human herpesvirus 5 Molecular cloning Protein sequences Vaccines cDNA sequences (US28 and homolog expression by <b>cytomegaloviruses</b> and its interaction with chemokines as a basis to prevent <b>cytomegalovirus</b> infection and dissemination)				
IT	Chemokines				

Eotaxin

Macrophage inflammatory protein 1 $\alpha$

Macrophage inflammatory protein 1 $\beta$

Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-2

RANTES (chemokine)

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(US28 and homolog expression by **cytomegaloviruses** and its

interaction with chemokines as a basis to prevent

**cytomegalovirus** infection and dissemination)

IT Proteins

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);

THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);

USES (Uses)

(US28; US28 and homolog expression by **cytomegaloviruses** and

its interaction with chemokines as a basis to prevent

**cytomegalovirus** infection and dissemination)

IT Proteins

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);

THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);

USES (Uses)

(US33; US28 and homolog expression by **cytomegaloviruses** and

its interaction with chemokines as a basis to prevent

**cytomegalovirus** infection and dissemination)

IT Proteins

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);

THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);

USES (Uses)

(US78; US28 and homolog expression by **cytomegaloviruses** and

its interaction with chemokines as a basis to prevent

**cytomegalovirus** infection and dissemination)

IT Nucleic acid amplification (method)

(determination of viral titer by; US28 and homolog expression by

**cytomegaloviruses** and its interaction with chemokines as a

basis to prevent **cytomegalovirus** infection and dissemination)

IT Blood analysis

Saliva

Urine analysis

(determination of viral titer in; US28 and homolog expression by

**cytomegaloviruses** and its interaction with chemokines as a

basis to prevent **cytomegalovirus** infection and dissemination)

IT Chemokines

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(fractalkines; US28 and homolog expression by **cytomegaloviruses**

and its interaction with chemokines as a basis to prevent

**cytomegalovirus** infection and dissemination)

IT Animal

Primates

(screening for active agents in; US28 and homolog expression by

**cytomegaloviruses** and its interaction with chemokines as a

basis to prevent **cytomegalovirus** infection and dissemination)

IT Antisense DNA

Ribozymes

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(targeting US28; US28 and homolog expression by

**cytomegaloviruses** and its interaction with chemokines as a

basis to prevent **cytomegalovirus** infection and dissemination)

IT 13448-22-1, Octoclotheptine

RL: PAC (Pharmacological activity); BIOL (Biological study)

(US28 and homolog expression by **cytomegaloviruses** and its

interaction with chemokines as a basis to prevent

**cytomegalovirus** infection and dissemination)

IT 403674-88-4 403674-90-8 403674-92-0 403674-94-2 403674-96-4

403674-98-6 403675-00-3 403675-02-5 403675-04-7 403675-06-9  
403675-08-1 403675-10-5 403675-12-7

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);  
THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);  
USES (Uses)

(amino acid sequence; US28 and homolog expression by  
**cytomegaloviruses** and its interaction with chemokines as a  
basis to prevent **cytomegalovirus** infection and dissemination)

IT 403674-87-3 403674-89-5 403674-91-9 403674-93-1 403674-95-3  
403674-97-5 403674-99-7 403675-01-4 403675-03-6 403675-05-8  
403675-07-0 403675-09-2 403675-11-6

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);  
THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);  
USES (Uses)

(nucleotide sequence; US28 and homolog expression by  
**cytomegaloviruses** and its interaction with chemokines as a  
basis to prevent **cytomegalovirus** infection and dissemination)

IT 403679-03-8 403679-04-9 403679-05-0 403679-06-1 403679-07-2  
403679-08-3 403679-09-4 403679-10-7 403679-11-8 403679-12-9  
403679-13-0 403679-14-1 403679-15-2 403679-16-3 403679-17-4  
403679-18-5 403679-19-6 403679-20-9 403679-21-0 403679-22-1  
403679-23-2

RL: PRP (Properties)

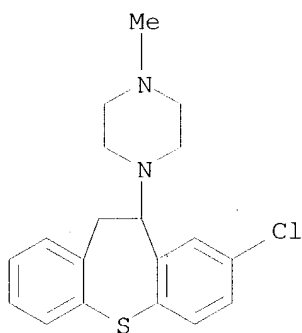
(unclaimed nucleotide sequence; uS28 and homolog expression by  
**cytomegaloviruses** and its interaction with chemokines as a  
basis to prevent **cytomegalovirus** infection and dissemination)

IT 13448-22-1, Octoclotheptine

RL: PAC (Pharmacological activity); BIOL (Biological study)  
(US28 and homolog expression by **cytomegaloviruses** and its  
interaction with chemokines as a basis to prevent  
**cytomegalovirus** infection and dissemination)

RN 13448-22-1 HCAPLUS

CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-  
(8CI, 9CI) (CA INDEX NAME)



L21 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:171670 HCAPLUS

DN 136:210544

ED Entered STN: 08 Mar 2002

TI Modulators of US28 chemokine receptors and their use for blocking  
**cytomegalovirus** dissemination

IN Schall, Thomas J.; McMaster, Brian E.; Dairaghi, Daniel J.

PA Chemocentryx, Inc., USA

SO PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00  
 CC 1-5 (Pharmacology)  
 FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002017900	A2	20020307	WO 2001-US27363	20010830
	WO 2002017900	A3	20030626		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2001087043	A5	20020313	AU 2001-87043	20010830
	US 2002127544	A1	20020912	US 2001-944163	20010830
PRAI	US 2000-228974P	P	20000830		
	US 2000-229191P	P	20000830		
	US 2000-229365P	P	20000830		
	WO 2001-US27363	W	20010830		

OS MARPAT 136:210544

AB Assays, compns. and methods of treatment are provided for modulating the binding of chemokines to US28 chemokine receptors on the surface of cells. In one aspect, the present invention provides an assay for identifying a compound useful for blocking **cytomegalovirus (CMV)** dissemination in a host by determining whether the compound inhibits the binding

of a chemokine to US28 or a US28 fragment. Typically, the assay will be run as a competitive binding assay using a labeled chemokine. A variety of chemokines are known to bind to US28 and are useful in this aspect of the invention. Preferably, the chemokine is fractalkine and the assay is a radioligand binding assay. In another aspect, the present invention provides methods for blocking **CMV** dissemination in a host by administering to the host an effective amount of a compound which blocks the binding of a chemokine to US28. Preferably, the compound is one which was identified using an assay of the present invention. In yet another aspect, the present invention provides pharmaceutical compns. for the treatment of **CMV** comprising compds. identified in the present assays.

ST US28 chemokine receptor modulator **cytomegalovirus** dissemination

IT Chemokine receptors

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
 (US28; modulators of US28 chemokine receptors and their use for blocking **cytomegalovirus** dissemination)

IT Drug delivery systems

(carriers; modulators of US28 chemokine receptors and their use for blocking **cytomegalovirus** dissemination)

IT Cell migration

(decrease in **cytomegalovirus**-infected cells; modulators of US28 chemokine receptors and their use for blocking **cytomegalovirus** dissemination)

IT Indicators

(for fractalkine; modulators of US28 chemokine receptors and their use for blocking **cytomegalovirus** dissemination)

IT Chemokines

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
 (fractalkines; modulators of US28 chemokine receptors and their use for blocking **cytomegalovirus** dissemination)

IT Antiviral agents

**Cytomegalovirus**

## Drug screening

(modulators of US28 chemokine receptors and their use for blocking  
**cytomegalovirus** dissemination)

IT Chemokines

Macrophage inflammatory protein 1 $\alpha$ Macrophage inflammatory protein 1 $\beta$ 

Monocyte chemoattractant protein-1

RANTES (chemokine)

RL: BSU (Biological study, unclassified); BUU (Biological use,  
unclassified); BIOL (Biological study); USES (Uses)

(modulators of US28 chemokine receptors and their use for blocking  
**cytomegalovirus** dissemination)

IT 4789-68-8, Octoclothepein maleate 13448-22-1,

Octoclothepein 20229-30-5, Methiothepein 74611-28-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)

(modulators of US28 chemokine receptors and their use for blocking  
**cytomegalovirus** dissemination)

IT 4789-68-8, Octoclothepein maleate 13448-22-1,

Octoclothepein 20229-30-5, Methiothepein 74611-28-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)

(modulators of US28 chemokine receptors and their use for blocking  
**cytomegalovirus** dissemination)

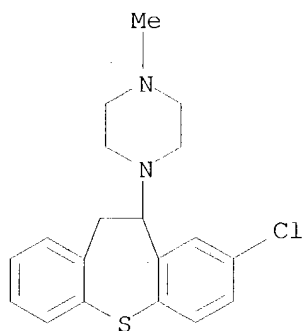
RN 4789-68-8 HCAPLUS

CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-,  
(2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 13448-22-1

CMF C19 H21 Cl N2 S

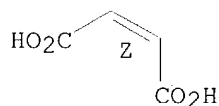


CM 2

CRN 110-16-7

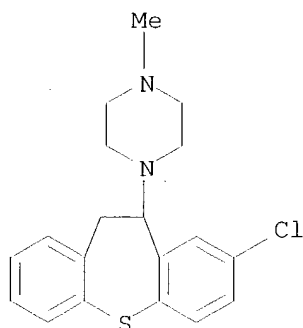
CMF C4 H4 O4

Double bond geometry as shown.

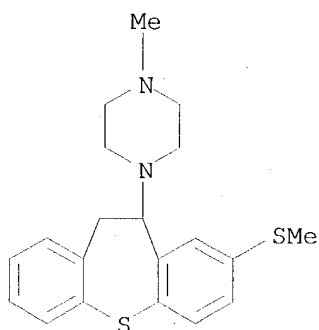




RN 13448-22-1 HCAPLUS  
CN Piperazine, 1-(8-chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-  
(8CI, 9CI) (CA INDEX NAME)



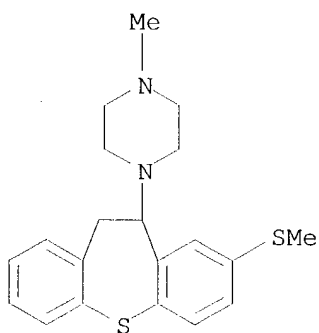
RN 20229-30-5 HCAPLUS  
CN Piperazine, 1-[10,11-dihydro-8-(methylthio)dibenzo[b,f]thiepin-10-yl]-4-methyl- (8CI, 9CI) (CA INDEX NAME)



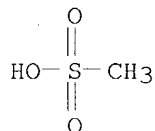
RN 74611-28-2 HCAPLUS  
CN Piperazine, 1-[10,11-dihydro-8-(methylthio)dibenzo[b,f]thiepin-10-yl]-4-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 20229-30-5  
CMF C20 H24 N2 S2



CM 2

CRN 75-75-2  
CMF C H4 O3 S

=> fil medline biosis  
FILE 'MEDLINE' ENTERED AT 08:50:44 ON 30 JAN 2004

FILE 'BIOSIS' ENTERED AT 08:50:44 ON 30 JAN 2004  
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=> d all tot 145

L45 ANSWER 1 OF 16 MEDLINE on STN DUPLICATE 1  
AN 2003429548 MEDLINE  
DN 22850808 PubMed ID: 12970425  
TI Characterization of the rhesus **cytomegalovirus** US28 locus.  
AU **Penfold M E T**; Schmidt T L; Dairaghi D J; Barry P A; **Schall T J**  
CS ChemoCentryx, San Carlos, California 94070, USA..  
mpenfold@chemocentryx.com  
SO JOURNAL OF VIROLOGY, (2003 Oct) 77 (19) 10404-13.  
Journal code: 0113724. ISSN: 0022-538X.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200310  
ED Entered STN: 20030913  
Last Updated on STN: 20031015  
Entered Medline: 20031014  
AB Human **cytomegalovirus** (CMV) US28 (and the related open reading frame [ORF] US27) are G-protein-coupled receptor homologs believed to play a role in viral pathogenesis. In vitro, US28 has been shown to bind and internalize ligands, as well as activate intracellular signaling in response to certain chemokines, and to initiate the migration of smooth muscle cells to chemokine gradients. To assess the role of US28 in vivo, we examined the rhesus model and sequenced and characterized the rhesus **CMV** US28 locus. We found that rhesus **CMV** carries five tandem homologs of US28, all widely divergent from US28 and from each other. By reverse transcription-PCR and Northern analysis, we demonstrated expression of these ORFs in infected cells. With stable cell lines expressing these ORFs, we analyzed the homolog's binding and signaling characteristics across a wide range of chemokines and found one (RhUS28.5) to have a ligand binding profile similar to that of US28. In addition, we localized US28 and the rhesus **CMV** homolog RhUS28.5 to the envelope of infectious virions, suggesting a role in viral entry or cell tropism.  
CT Check Tags: Animal; Human  
Amino Acid Sequence  
Calcium: ME, metabolism  
Chromosome Mapping  
Immediate-Early Proteins: GE, genetics

\*Macaca mulatta: VI, virology  
Molecular Sequence Data  
Open Reading Frames  
Receptors, Chemokine: CH, chemistry  
\*Receptors, Chemokine: GE, genetics  
Receptors, Chemokine: PH, physiology  
Viral Proteins: CH, chemistry  
\*Viral Proteins: GE, genetics  
Viral Proteins: PH, physiology  
RN 7440-70-2 (Calcium)  
CN 0 (Immediate-Early Proteins); 0 (Receptors, Chemokine); 0 (US28 receptor);  
0 (US3 protein, **cytomegalovirus**); 0 (Viral Proteins)

L45 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 2  
AN 2003572736 MEDLINE  
DN PubMed ID: 14644603  
TI A macrophage inflammatory protein homolog encoded by guinea pig  
**cytomegalovirus** signals via CC chemokine receptor 1.  
AU **Penfold Mark**; Miao Zhenhua; Wang Yu; Haggerty Shannon; Schleiss  
Mark R  
CS ChemoCentryx, San Carlos, CA 94070, USA.  
NC HD044864-01 (NICHD)  
SO Virology, (2003 Nov 25) 316 (2) 202-12.  
Journal code: 0110674. ISSN: 0042-6822.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200401  
ED Entered STN: 20031216  
Last Updated on STN: 20040107  
Entered Medline: 20040106

AB **Cytomegaloviruses** encode homologs of cellular immune effector  
proteins, including chemokines (CKs) and CK receptor-like G  
protein-coupled receptors (GPCRs). Sequence of the guinea pig  
**cytomegalovirus** (GPCMV) genome identified an open reading frame  
(ORF) which predicted a 101 amino acid (aa) protein with homology to the  
macrophage inflammatory protein (MIP) subfamily of CC (beta) CKs,  
designated GPCMV-MIP. To assess functionality of this CK, recombinant  
GPCMV-MIP was expressed in HEK293 cells and assayed for its ability to  
bind to and functionally interact with a variety of GPCRs. Specific  
signaling was observed with the hCCR1 receptor, which could be blocked  
with hMIP -1alpha in competition experiments. Migration assays revealed  
that GPCMV-MIP was able to induce chemotaxis in hCCR1-L1.2 cells.  
Antisera raised against a GST-MIP fusion protein immunoprecipitated  
species of approximately 12 and 10 kDa from GPCMV-inoculated tissue  
culture lysates, and convalescent antiserum from GPCMV-infected animals  
was immunoreactive with GST-MIP by ELISA assay. These results represent  
the first substantive in vitro characterization of a functional CC CK  
encoded by a **cytomegalovirus**.

CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.  
Amino Acid Sequence  
Animals  
Calcium: ME, metabolism  
Cell Movement  
Guinea Pigs  
Macrophage Inflammatory Proteins: CH, chemistry  
Macrophage Inflammatory Proteins: GE, genetics  
\*Macrophage Inflammatory Proteins: PH, physiology  
Molecular Sequence Data  
\*Receptors, Chemokine: PH, physiology  
Roseolovirus: GE, genetics  
\*Roseolovirus: IM, immunology

\*Signal Transduction: PH, physiology

Viral Proteins: CH, chemistry

Viral Proteins: GE, genetics

\*Viral Proteins: PH, physiology

RN 7440-70-2 (Calcium)

CN 0 (CC chemokine receptor 1); 0 (Macrophage Inflammatory Proteins); 0 (Receptors, Chemokine); 0 (Viral Proteins)

L45 ANSWER 3 OF 16 MEDLINE on STN DUPLICATE 3

AN 2002051344 MEDLINE

DN PubMed ID: 11773404

TI Potent immunosuppressive activities of **cytomegalovirus**-encoded interleukin-10.

CM Erratum in: J Virol 2002 Apr;76(7):3585

AU Spencer Juliet V; Lockridge Kristen M; Barry Peter A; Lin Gaofeng; Tsang Monica; **Penfold Mark E T**; **Schall Thomas J**

CS ChemoCentryx, San Carlos, California 94070, USA.

NC 1-R01-HL57883 (NHLBI)

SO Journal of virology, (2002 Feb) 76 (3) 1285-92.

Journal code: 0113724. ISSN: 0022-538X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200202

ED Entered STN: 20020125

Last Updated on STN: 20020420

Entered Medline: 20020212

AB **Cytomegalovirus (CMV)** has highly evolved mechanisms for avoiding detection by the host immune system. Recently, in the genomes of human and primate **CMV**, a novel gene comprising segments of noncontiguous open reading frames was identified and found to have limited predicted homology to endogenous cellular interleukin-10 (IL-10). Here we investigate the biological activities of the **CMV** IL-10-like gene product and show it to possess potent immunosuppressive properties. Both purified bacterium-derived recombinant **CMV** IL-10 and **CMV** IL-10 expressed in supernatants of human cells were found to inhibit proliferation of mitogen-stimulated peripheral blood mononuclear cells (PBMCs), with specific activity comparable to that of recombinant human IL-10. In addition, **CMV** IL-10 expressed from human cells inhibited cytokine synthesis, as treatment of stimulated PBMCs and monocytes with **CMV** IL-10 led to a marked decrease in production of proinflammatory cytokines. Finally, **CMV** IL-10 was observed to decrease cell surface expression of both major histocompatibility complex (MHC) class I and class II molecules, while conversely increasing expression of the nonclassical MHC allele HLA-G. These results demonstrate for the first time that **CMV** has a biologically active IL-10 homolog that may contribute to immune evasion during virus infection.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.

Animals

Cell Division

Cell Membrane: IM, immunology

Cells, Cultured

\***Cytomegalovirus: ME, metabolism**

Gene Expression

Genes, MHC Class I

Genes, MHC Class II

\*Immunosuppressive Agents

Interferon Type II: BI, biosynthesis

\*Interleukin-10: ME, metabolism

Leukocytes, Mononuclear: CY, cytology

Leukocytes, Mononuclear: DE, drug effects

Leukocytes, Mononuclear: ME, metabolism

Macaca mulatta

Receptors, Interleukin: ME, metabolism

Recombinant Proteins: ME, metabolism

Viral Proteins: GE, genetics

\*Viral Proteins: ME, metabolism

Viral Proteins: PD, pharmacology

RN 130068-27-8 (Interleukin-10); 82115-62-6 (Interferon Type II)

CN 0 (CMV IL-10 protein, **Cytomegalovirus**); 0  
(Immunosuppressive Agents); 0 (Receptors, Interleukin); 0 (Recombinant  
Proteins); 0 (Viral Proteins); 0 (interleukin-10 receptor)

L45 ANSWER 4 OF 16 MEDLINE on STN DUPLICATE 4

AN 2001296913 MEDLINE

DN PubMed ID: 11376481

TI A review of genetic differences between limited and extensively passaged  
human **cytomegalovirus** strains.

AU Prichard M N; Penfold M E; Duke G M; Spaete R R; Kemble G W

CS Aviron, 297 N. Bernardo Avenue, Mountain View, CA 94043, USA.

SO Reviews in medical virology, (2001 May-Jun) 11 (3) 191-200. Ref: 71  
Journal code: 9112448. ISSN: 1052-9276.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 200107

ED Entered STN: 20010716

Last Updated on STN: 20010716

Entered Medline: 20010712

AB The complete genetic content of human **cytomegalovirus** (HCMV) has  
been difficult to determine, since most strains studied in the laboratory  
have been extensively passaged in human fibroblast cultures which can  
change the genetic content as well as the biological properties of the  
virus. Approximately 13 kb of novel DNA sequences located near the right  
edge of the unique long (UL) component of the genome has been discovered  
in Toledo, clinical isolates and certain stocks of Towne. This region of  
novel sequence, designated the UL/b' region, encodes several interesting  
proteins including vCXC-1, a potent IL-8 homologue, and UL144, a member of  
the TNF receptor family. This region is missing from the prototypic  
laboratory variants of Towne and AD169. In contrast to Toledo and other  
low passage isolates which have relatively small repeats bracketing the UL  
component, the Towne and AD169 laboratory variants contain large (>10 kb)  
b/b' repeats. The large size of these repeats in AD169 and Towne appear  
to have arisen as compensation for the loss of sequences from the UL/b'  
region that existed in less passaged variants of these strains.  
Consequently, many of the haploid genes at the left edge of the prototypic  
wild-type (wt) UL component are diploid in AD169 and Towne. We  
hypothesise that this plasticity of the genome at the right edge of the UL  
component results from extensive passage and adaptation to replication in  
fibroblasts in vitro. Further work will be required to understand the  
complete genetic content of wt HCMV.

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CT Check Tags: Comparative Study; Human

Amino Acid Sequence

Cells, Cultured

Chemokines, CXC: GE, genetics

\***Cytomegalovirus**: GE, genetics

**Cytomegalovirus**: GD, growth & development

**Cytomegalovirus**: PY, pathogenicity

**Cytomegalovirus** Infections: VI, virology

Fibroblasts

\*Genome, Viral  
 Membrane Glycoproteins: GE, genetics  
 Molecular Sequence Data  
 Sequence Alignment  
 Variation (Genetics)  
 Viral Proteins: GE, genetics  
 Virus Cultivation  
 Virus Replication

CN 0 (Chemokines, CXC); 0 (Membrane Glycoproteins); 0 (UL144 ORF protein, Human herpesvirus 5); 0 (Viral Proteins); 0 (viral chemokine CXC-1)

L45 ANSWER 5 OF 16 MEDLINE on STN DUPLICATE 5  
 AN 1999415953 MEDLINE  
 DN PubMed ID: 10485920  
 TI **Cytomegalovirus**-encoded beta chemokine promotes monocyte-associated viremia in the host.  
 AU Saederup N; Lin Y C; Dairaghi D J; **Schall T J**; Mocarski E S  
 CS Department of Microbiology and Immunology, Stanford University Medical School, Stanford, CA 94305-5124, USA.  
 NC R01 AI28341 (NIAID)  
 R01 AI30363 (NIAID)  
 T32 GM07328 (NIGMS)  
 SO Proceedings of the National Academy of Sciences of the United States of America, (1999 Sep 14) 96 (19) 10881-6.  
 Journal code: 7505876. ISSN: 0027-8424.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199910  
 ED Entered STN: 19991026  
 Last Updated on STN: 19991026  
 Entered Medline: 19991014

AB Chemokine homologs are encoded by many large DNA viruses, suggesting that they contribute to control of host leukocyte transmigration and trafficking during viral infection. Murine **cytomegalovirus** carries a CC (beta) chemokine homolog gene giving rise to two related proteins, murine **cytomegalovirus** chemokine 1 and 2 (MCK-1 and MCK-2). MCK-1 peptide was found to induce calcium signaling and adherence in murine peritoneal macrophages. Cells bearing human chemokine receptor CCR3 and the human macrophage THP1 cell line were responsive to MCK-1. This pattern suggested that MCK-1 might act as an agonist, promoting leukocyte trafficking during viral infection. Consistent with this prediction, MCK-1/MCK-2 mutant viruses exhibit dramatically reduced peak levels of monocyte-associated viremia in experimentally infected mice. Thus, MCK-1/MCK-2 appears to promote host leukocyte migration to initial sites of infection and may be responsible for attracting monocytes or macrophages that efficiently disseminate virus in the host.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.  
 Amino Acid Sequence  
 Animals  
 Calcium: ME, metabolism  
 \*Chemokines: GE, genetics  
 \*Chemokines: ME, metabolism  
 Chemokines, CC: GE, genetics  
 \*Chemokines, CC: PH, physiology  
 \***Cytomegalovirus: GE, genetics**  
 \***Cytomegalovirus: ME, metabolism**  
 Mice  
 Mice, Inbred BALB C  
 Models, Biological  
 Models, Genetic  
 Molecular Sequence Data

\*Monocytes: ME, metabolism  
 Monocytes: VI, virology  
 Peritoneum: ME, metabolism  
 Peritoneum: VI, virology  
 Recombination, Genetic  
 Sequence Homology, Amino Acid  
 Time Factors

\*Viremia: GE, genetics  
 Viremia: ME, metabolism

RN 7440-70-2 (Calcium)

CN 0 (Chemokines); 0 (Chemokines, CC); 0 (MCK-1 protein); 0 (MCK-2 protein,  
 Mouse **cytomegalovirus** 1)

L45 ANSWER 6 OF 16 MEDLINE on STN

DUPLICATE 6

AN 1999380606 MEDLINE

DN 99380606 PubMed ID: 10449781

TI **Cytomegalovirus** encodes a potent alpha chemokine.

AU **Penfold M E**; Dairaghi D J; Duke G M; Saederup N; Mocarski E S;  
 Kemble G W; **Schall T J**

CS Aviron, 297 Bernardo Avenue, Mountain View, CA 94043, USA..  
 mpenfold@aviron.com

NC AI30363 (NIAID)

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF  
 AMERICA, (1999 Aug 17) 96 (17) 9839-44.  
 Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

OS GENBANK-U33331

EM 199909

ED Entered STN: 19990925

Last Updated on STN: 19990925

Entered Medline: 19990909

AB **Cytomegalovirus** is a widespread opportunistic pathogen affecting immunocompromised individuals in whom neutrophils may mediate virus dissemination and contribute to progression of disease. Recent sequence analysis suggests that genes absent or altered in attenuated strains may influence pathogenesis. We have found two genes, UL146 and UL147, whose products have sequence similarity to alpha (CXC) chemokines. UL146 encodes a protein, designated vCXC-1, that is a 117-aa glycoprotein secreted into the culture medium as a late gene product, where its presence correlates with the ability to attract human neutrophils. Recombinant vCXC-1 is a fully functional chemokine, inducing calcium mobilization, chemotaxis, and degranulation of neutrophils. High-affinity vCXC-1 binding is shown to be mediated via CXCR2, but not CXCR1. vCXC-1 exhibits a potency approaching that of human IL-8. As the first example of a virus-encoded alpha chemokine, vCXC-1 may ensure the active recruitment of neutrophils during **cytomegalovirus** infection, thereby providing for efficient dissemination during acute infection and accounting for the prominence of this leukocyte subset in **cytomegalovirus** disease.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.

Amino Acid Sequence

Chemokines, CXC: CH, chemistry

Chemokines, CXC: GE, genetics

\*Chemokines, CXC: ME, metabolism

Cloning, Molecular

**Cytomegalovirus: GE, genetics**

**\*Cytomegalovirus: ME, metabolism**

**\*Cytomegalovirus Infections: ME, metabolism**

DNA, Viral: CH, chemistry

Fibroblasts: ME, metabolism

Fibroblasts: VI, virology  
 Lung: CY, cytology  
 Molecular Sequence Data  
 \*Receptors, Chemokine: ME, metabolism  
 \*Receptors, Interleukin: ME, metabolism  
 Receptors, Interleukin-8B

CN 0 (Chemokines, CXC); 0 (DNA, Viral); 0 (Receptors, Chemokine); 0 (Receptors, Interleukin); 0 (Receptors, Interleukin-8B); 0 (viral chemokine CXC-1)

L45 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 7  
 AN 1998406221 MEDLINE  
 DN 98406221 PubMed ID: 9733857  
 TI Functional analysis of the human **cytomegalovirus** US28 gene by insertion mutagenesis with the green fluorescent protein gene.  
 AU Vieira J; Schall T J; Corey L; Geballe A P  
 CS Department of Laboratory Medicine, University of Washington, Seattle, Washington 98195, USA.. vieiraj@u.washington.edu  
 NC AI26672 (NIAID)  
 SO JOURNAL OF VIROLOGY, (1998 Oct) 72 (10) 8158-65.  
 Journal code: 0113724. ISSN: 0022-538X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199810  
 ED Entered STN: 19981020  
 Last Updated on STN: 19981020  
 Entered Medline: 19981007

AB The protein encoded by the US28 gene of human **cytomegalovirus** (HCMV) has homology to G protein-coupled receptors (GCR). Previous studies demonstrated that recombinant US28 protein can bind the beta class of chemokines (K. Neote, D. DiGregorio, J. Y. Mak, R. Horuk, and T. J. Schall, Cell 72:415-425, 1993) and induce a rise in intracellular calcium after the binding of chemokines (J. L. Gao and P. M. Murphy, J. Biol. Chemical 269:28539-28542, 1994). In order to investigate the function of the US28 protein in virus-infected cells, a recombinant HCMV (HV5.8) was constructed, with the US28 open reading frame disrupted by the insertion of the Escherichia coli gpt gene and the gene for the green fluorescent protein. The US28 gene is not required for growth in human fibroblasts (HF). HF infected with wild-type HCMV bound RANTES at 24 h postinfection and demonstrated an intracellular calcium flux induced by RANTES. In cells infected with HV5.8, RANTES did not bind or induce a calcium flux, demonstrating that US28 is responsible for the beta-chemokine binding and induced calcium signaling in HCMV-infected cells. The ability of the US28 gene to bind chemokines was shown to cause a significant reduction in the concentration of RANTES in the medium of infected cells. Northern analysis of RNA from infected cells showed that US28 is an early gene, while US27 (another GCR) is a late gene.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.  
 Blotting, Northern  
 Calcium: ME, metabolism  
 Cells, Cultured  
 \*Cytomegalovirus: GE, genetics  
 Ion Transport  
 \*Luminescent Proteins: GE, genetics  
 Mutagenesis, Site-Directed  
 RANTES: ME, metabolism  
 RNA, Viral: GE, genetics  
 \*Receptors, Chemokine: GE, genetics  
 Receptors, Chemokine: ME, metabolism  
 Recombinant Proteins: GE, genetics

RN 147336-22-9 (green fluorescent protein); 156286-78-1 (monocyte



chemoattractant protein 1 receptor); 7440-70-2 (Calcium)  
 CN 0 (Luminescent Proteins); 0 (RANTES); 0 (RNA, Viral); 0 (Receptors, Chemokine); 0 (Recombinant Proteins)

L45 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 8  
 AN 1998362100 MEDLINE  
 DN 98362100 PubMed ID: 9696791  
 TI Identification of persistent RNA-DNA hybrid structures within the origin of replication of human **cytomegalovirus**.  
 AU Prichard M N; Jairath S; **Penfold M E**; St Jeor S; Bohlman M C; Pari G S  
 CS Iconix Pharmaceuticals, Inc., Mountain View, California 94043, USA.  
 SO JOURNAL OF VIROLOGY, (1998 Sep) 72 (9) 6997-7004.  
 Journal code: 0113724. ISSN: 0022-538X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199809  
 ED Entered STN: 19980925  
 Last Updated on STN: 19980925  
 Entered Medline: 19980916

AB Human **cytomegalovirus** (HCMV) lytic-phase DNA replication initiates at the cis-acting origin of replication, oriLyt. oriLyt is a structurally complex region containing repeat elements and transcription factor binding sites. We identified two site-specific alkali-labile regions within oriLyt which flank an alkali-resistant DNA segment. These alkali-sensitive regions were the result of the degradation of two RNA species embedded within oriLyt and covalently linked to viral DNA. The virus-associated RNA, vRNA, was identified by DNase I treatment of HCMV DNA obtained from sucrose gradient purified virus. This heterogeneous population of vRNA was end labeled and used as a hybridization probe to map the exact location of vRNAs within oriLyt. vRNA-1 is localized between restriction endonuclease sites XhoI at nucleotide (nt) 93799 and SacI at nt 94631 and is approximately 500 bases long. The second vRNA, vRNA-2, lies within a region which exhibits a heterogeneous restriction pattern located between the SphI (nt 92636) and BamHI (nt 93513) and is approximately 300 bases long. This region was previously shown to be required for oriLyt replication (D. G. Anders, M. A. Kacica, G. S. Pari, and S. M. Punturieri, J. Virol. 66:3373-3384, 1992). RNase H analysis determined that vRNA-2 forms a persistent RNA-DNA hybrid structure in the context of the viral genome and in an oriLyt-containing plasmid used in the transient-replication assay.

CT Check Tags: Human  
 Binding Sites  
 Cell Line  
 Chromosome Mapping  
 \***Cytomegalovirus: GE, genetics**  
 \*DNA, Viral  
 Nucleic Acid Conformation  
 \*RNA, Viral  
 \*Recombination, Genetic  
 \*Replication Origin  
 Restriction Mapping  
 Sodium Hydroxide

RN 1310-73-2 (Sodium Hydroxide)  
 CN 0 (DNA, Viral); 0 (RNA, Viral)

L45 ANSWER 9 OF 16 MEDLINE on STN DUPLICATE 9  
 AN 1998087825 MEDLINE  
 DN 98087825 PubMed ID: 9426445  
 TI Formation of **cytomegalovirus** DNA replication compartments defined by localization of viral proteins and DNA synthesis.

AU **Penfold M E**; Mocarski E S  
 CS Department of Microbiology and Immunology, Stanford University, California  
 94305-5124, USA.  
 NC AI20211 (NIAID)  
 SO VIROLOGY, (1997 Dec 8) 239 (1) 46-61.  
 Journal code: 0110674. ISSN: 0042-6822.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199801  
 ED Entered STN: 19980206  
 Last Updated on STN: 19980206  
 Entered Medline: 19980129  
 AB To characterize the formation of replication compartments in human  
**cytomegalovirus**-infected cells, and to determine the fate of newly  
 synthesized DNA, we localized viral replication proteins and DNA synthesis  
 at early and late times during infection. As expected, ppUL57  
 (single-stranded DNA binding protein) and ppUL44 (DNA polymerase  
 processivity factor) both localized to replication compartments beginning  
 at 48 hpi. BrdU was incorporated into viral DNA in these compartments  
 that was found to mature into progeny virus based on our ability to chase  
 the label into the cytoplasm and out of the cell over the ensuing 72-h  
 period. Although the pattern of BrdU incorporation at early times (20 or  
 24 hpi) was punctate, and distinct from the replication compartment that  
 formed later during infection, viral DNA synthesized at this time also  
 matured into progeny virus during a chase. Interestingly, sites of ppUL57  
 localization did not overlap completely with sites of BrdU incorporation  
 at early times. Products from the UL112-113 gene localized to subnuclear  
 regions by 6 hpi, earlier than ppUL57. Between 12 and 24 hpi, both ppUL57  
 and ppUL44 joined UL112-113 gene products at sites that subsequently  
 developed into replication compartments. When infection was carried out  
 in the presence of phosphonoformate or ganciclovir, replication  
 compartment formation was blocked. A viral mutant deficient in uracil DNA  
 glycosidase, previously shown to exhibit a delay in the initial phase of  
 DNA replication, also exhibited delayed formation of replication  
 compartments. These results raise the possibility that subnuclear sites  
 defined by UL112-113 localization orchestrate the assembly of the  
**CMV** replication compartment and implicate punctate sites of BrdU  
 incorporation as sites of early viral DNA replication that precedes the  
 formation of the replication compartment.  
 CT Check Tags: Human; Support, U.S. Gov't, P.H.S.  
 Cell Compartmentation  
 Cell Line  
 \*Cytomegalovirus: PH, physiology  
 \*DNA Replication  
 \*DNA, Viral: GE, genetics  
 Microscopy, Confocal  
 \*Viral Proteins: PH, physiology  
 Virus Replication  
 CN 0 (DNA, Viral); 0 (Viral Proteins)  
 L45 ANSWER 10 OF 16 MEDLINE on STN DUPLICATE 10  
 AN 93161416 MEDLINE  
 DN 93161416 PubMed ID: 7679328  
 TI Molecular cloning, functional expression, and signaling characteristics of  
 a C-C chemokine receptor.  
 AU Neote K; DiGregorio D; Mak J Y; Horuk R; **Schall T J**  
 CS Department of Immunology, Genentech, Incorporated, South San Francisco,  
 California 94080.  
 SO CELL, (1993 Feb 12) 72 (3) 415-25.  
 Journal code: 0413066. ISSN: 0092-8674.  
 CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 OS GENBANK-L09230; GENBANK-L20501; GENBANK-L33702; GENBANK-L33703;  
 GENBANK-L33704; GENBANK-L33705; GENBANK-L33706; GENBANK-L33707;  
 GENBANK-L33708; GENBANK-L33709; GENBANK-M99293; GENBANK-X17403  
 EM 199303  
 ED Entered STN: 19930402  
 Last Updated on STN: 19970203  
 Entered Medline: 19930316  
 AB The immunoregulatory proteins C-C chemokines are potent chemoattractants of lymphocytes and monocytes, as well as activators and attractants of eosinophils and basophils. We have isolated a cDNA that encodes a seven transmembrane-spanning receptor, with homology to other chemoattractant receptors, that encodes a protein designated C-C CKR-1 that acts as a receptor for the C-C chemokines. Human and murine macrophage inflammatory protein 1 alpha (MIP-1 alpha), human human monocyte chemotactic protein 1 (MCP-1), and RANTES all bind to the C-C CKR-1 with varying affinities. Chemokine binding affinity does not predict how well the ligand will transmit a signal through the receptor: RANTES and human MIP-1 alpha induce a similar intracellular calcium flux while binding with disparate affinities, while MCP-1 and human MIP-1 beta induce calcium mobilization only at high concentrations. Finally, C-C chemokines were shown to bind a C-C CKR-1-related gene product encoded by **cytomegalovirus**, suggesting a role for C-C chemokines in viral immunity.  
 CT Check Tags: Human; In Vitro  
 Amino Acid Sequence  
 Binding, Competitive  
 Calcium: PH, physiology  
 Cells, Cultured  
 Cloning, Molecular  
 \*Cytokines: PH, physiology  
   **Cytomegalovirus: ME, metabolism**  
 DNA: GE, genetics  
 Genes, Structural, Viral  
 \*Lymphokines: PH, physiology  
 Macrophage Inflammatory Protein-1  
 Molecular Sequence Data  
 \*Monokines: PH, physiology  
 Oligopeptides: CH, chemistry  
 Open Reading Frames  
 RANTES  
 \*Receptors, Cell Surface: GE, genetics  
 Receptors, Cell Surface: PH, physiology  
 Sequence Alignment  
 Signal Transduction  
 Viral Proteins: ME, metabolism  
 RN 7440-70-2 (Calcium); 9007-49-2 (DNA)  
 CN 0 (Cytokines); 0 (Lymphokines); 0 (Macrophage Inflammatory Protein-1); 0 (Monokines); 0 (Oligopeptides); 0 (RANTES); 0 (Receptors, Cell Surface); 0 (Viral Proteins)  
 GEN C5AR; CKR-1; FMLPR; IL8RA; IL8RB; STSR  
 L45 ANSWER 11 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
 AN 2003:260926 BIOSIS  
 DN PREV200300260926  
 TI A novel **cytomegalovirus**-encoded chemokine signals via CC chemokine receptor 1 (CCR1).  
 AU Schleiss, Mark R. [Reprint Author]; Haggerty, Shannon; Wang, Yu; Miao, Zhenua; **Penfold, Mark**  
 CS Division of Infectious Diseases, Children's Hospital Research Foundation, Cincinnati, OH, USA  
 SO Pediatric Research, (April 2003) Vol. 53, No. 4 Part 2, pp. 349A. print.

Meeting Info.: Annual Meeting of the Pediatric Academic Societies'.  
Seattle, WA, USA. May 03-06, 2003. Pediatric Academic Societies.  
ISSN: 0031-3998 (ISSN print).

DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 4 Jun 2003  
Last Updated on STN: 4 Jun 2003

CC General biology - Symposia, transactions and proceedings 00520  
Genetics - General 03502  
Genetics - Animal 03506  
Genetics - Human 03508  
Endocrine - General 17002  
Genetics of bacteria and viruses 31500  
Virology - General and methods 33502  
Medical and clinical microbiology - Virology 36006

IT Major Concepts  
Infection; Molecular Genetics (Biochemistry and Molecular Biophysics)

IT Diseases  
cytomegalovirus infection: viral disease.  
Cytomegalovirus Infections (MeSH)

IT Chemicals & Biochemicals  
CC chemokine receptor 1; chemokines; macrophage inflammatory  
protein-1-alpha

IT Miscellaneous Descriptors  
viral genome

ORGN Classifier  
Herpesviridae 03115  
Super Taxa  
dsDNA Viruses; Viruses; Microorganisms  
Organism Name  
Cytomegalovirus (genus): pathogen  
Taxa Notes  
Double-Stranded DNA Viruses, Microorganisms, Viruses

ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
HEK293 cell line (cell line)  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier  
Caviidae 86300  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
guinea-pig (common): host, animal model  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
Rodents, Vertebrates

GEN cytomegalovirus MIP gene [cytomegalovirus macrophage  
inflammatory protein gene] (Herpesviridae): deletion

L45 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
AN 2000:493692 BIOSIS  
DN PREV200000493813  
TI Interplay between the 'endogenous' and 'infectious' chemokine systems.  
AU Schall, Thomas [Reprint author]  
CS ChemoCentryx, San Carlos, CA, USA  
SO Journal of Human Virology, (September-October, 2000) Vol. 3, No. 5, pp.  
239. print.  
Meeting Info.: 2000 International Meeting of the Institute of Human

Virology. Baltimore, Maryland, USA. September 10-15, 2000.  
ISSN: 1090-9508.

DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 15 Nov 2000  
Last Updated on STN: 10 Jan 2002  
CC Endocrine - General 17002  
General biology - Symposia, transactions and proceedings 00520  
Pathology - General 12502  
Virology - Animal host viruses 33506  
Immunology - General and methods 34502  
Immunology - Immunopathology, tissue immunology 34508  
Medical and clinical microbiology - Virology 36006  
IT Major Concepts  
Immune System (Chemical Coordination and Homeostasis); Infection  
IT Diseases  
autoimmune disease: immune system disease  
Autoimmune Diseases (MeSH)  
IT Chemicals & Biochemicals  
chemokine systems: analysis, endogenous, functions, infectious,  
interplay; chemokines  
IT Miscellaneous Descriptors  
autoimmunity; infections; inflammation; pathology; therapeutic  
intervention: molecular targets; Meeting Abstract

## ORGN Classifier

**Herpesviridae 03115**

Super Taxa

dsDNA Viruses; Viruses; Microorganisms

Organism Name

**cytomegalovirus**

human herpesvirus-8: pathogen

Taxa Notes

Double-Stranded DNA Viruses, Microorganisms, Viruses

## ORGN Classifier

Hominidae 86215

Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

human: host

Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L45 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 1999:470347 BIOSIS

DN PREV199900470347

TI HHV8-encoded vMIP-I selectively engages chemokine receptor CCR8. Agonist  
and antagonist profiles of viral chemokines.

AU Dairaghi, Daniel J.; Fan, Rong A.; McMaster, Brian E.; Hanley, Michael R.;  
**Schall, Thomas J.** [Reprint author]

CS ChemoCentryx, 1539 Industrial Rd., San Carlos, CA, 94070, USA

SO Journal of Biological Chemistry, (July 30, 1999) Vol. 274, No. 31, pp.  
21569-21574. print.

CODEN: JBCHA3. ISSN: 0021-9258.

DT Article

LA English

ED Entered STN: 9 Nov 1999

Last Updated on STN: 9 Nov 1999

AB Uncertainty regarding viral chemokine function is mirrored by an  
incomplete knowledge of host chemokine receptor usage by the virally  
encoded proteins. One such molecule is vMIP-I, a C-C type chemokine of  
undefined function and binding specificity, encoded by the Kaposi's  
sarcoma herpesvirus HHV-8. We report here that vMIP-I binds to and

induces cytosolic (Ca<sup>2+</sup>) signals in human T cells selectively through CCR8, a CC chemokine receptor associated with Th2 lymphocytes. Furthermore, using a panel of 65 different human, viral, and rodent chemokines, we have established a comprehensive ligand binding "fingerprint" for CCR8. The receptor exhibits marked "high" affinity (K<sub>d</sub> < 15 nM) only for four chemokines, three of them of viral origin: vMIP-I, vMIP-II, vMCC-I, and human I-309. A previously unreported second class of lower affinity ligands includes MCP-3 and possibly two other viral chemokines. vMIP-I and I-309 appear to act as CCR8 agonists: binding to and inducing cytosolic (Ca<sup>2+</sup>) elevation through the receptor. By contrast, vMIP-II and vMCC-I act as potent antagonists: binding without inducing signaling, and blocking the effects of I-309 and vMIP-I. These results suggest a ligand hierarchy for CCR8, identifying vMIP-I as a selective viral chemokine agonist. CCR8 may thus engage a specific subset of chemokines with the potential to regulate each other during viral infection and immune regulation.

CC Medical and clinical microbiology - General and methods 36001  
 Biochemistry studies - General 10060  
 Enzymes - General and comparative studies: coenzymes 10802  
 Blood - General and methods 15001  
 Immunology - General and methods 34502  
 General biology - Miscellaneous 00532  
 IT Major Concepts  
     Enzymology (Biochemistry and Molecular Biophysics); Infection  
 IT Parts, Structures, & Systems of Organisms  
     CCR8 chemokine receptor; Th2 lymphocyte: blood and lymphatics, immune system  
 IT Chemicals & Biochemicals  
     viral chemokines: agonist profile, antagonist profile; vMIP-II; vMIP-1  
 ORGN Classifier  
     **Herpesviridae 03115**  
     Super Taxa  
         dsDNA Viruses; Viruses; Microorganisms  
     Organism Name  
         human herpesvirus 8  
     Taxa Notes  
         Double-Stranded DNA Viruses, Microorganisms, Viruses

L45 ANSWER 14 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
 AN 1996:66311 BIOSIS  
 DN PREV199698638446

TI Herpes simplex virus protein targets for CD4 and CD8 lymphocyte cytotoxicity in cultured epidermal keratinocytes treated with interferon-gamma.

AU Mikloska, Zorka; Kesson, Alison M.; Penfold, Mark E. T.; Cunningham, Anthony L. [Reprint author]

CS Virol. Dep., ICPMR, Westmead Hosp., Westmead NSW 2145, Australia

SO Journal of Infectious Diseases, (1996) Vol. 173, No. 1, pp. 7-17.  
 CODEN: JIDIAQ. ISSN: 0022-1899.

DT Article

LA English

ED Entered STN: 9 Feb 1996

Last Updated on STN: 9 Feb 1996

AB In early recurrent herpetic lesions, CD4 T lymphocytes are the predominant infiltrating cells, and keratinocytes expressing major histocompatibility complex (MHC) class II antigens, induced by interferon-gamma (IFN-gamma), are the major site of herpes simplex virus (HSV) replication. IFN-gamma pretreatment of human keratinocytes in vitro reduced MHC class I antigen down-regulation by HSV-1 infection and induced expression of HLA-DR that was unaltered by subsequent HSV-1 infection. Incubation of these infected keratinocytes with phosphonoacetic acid (PAA) almost completely inhibited expression of four major HSV glycoproteins, although expression of early proteins was not affected. Weak CD8 T lymphocyte cytotoxicity against

IFN-gamma-stimulated, HLA-DR-expressing HSV-1-infected keratinocytes was consistently directed to the immediate early/early proteins (all 9 patients tested) but against late proteins to a lesser degree (4/9 patients). However, CD4 T lymphocyte cytotoxicity was much greater and directed predominantly against late HSV-1 glycoproteins (all 9 subjects tested) in these cells.

CC Cytology - Human 02508  
 Biochemistry studies - Proteins, peptides and amino acids 10064  
 Blood - Lymphatic tissue and reticuloendothelial system 15008  
 Pharmacology - Immunological processes and allergy 22018  
 In vitro cellular and subcellular studies 32600  
 Immunology - Bacterial, viral and fungal 34504  
 Medical and clinical microbiology - Virology 36006

IT Major Concepts  
 Blood and Lymphatics (Transport and Circulation); Cell Biology; Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology

IT Miscellaneous Descriptors  
 IMMUNOLOGIC-DRUG; INTERFERON-GAMMA; MAJOR HISTOCOMPATIBILITY COMPLEX

ORGN Classifier  
**Herpesviridae 03115**  
 Super Taxa  
 dsDNA Viruses; Viruses; Microorganisms  
 Organism Name  
 Herpesviridae  
 Taxa Notes  
 Double-Stranded DNA Viruses, Microorganisms, Viruses

ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L45 ANSWER 15 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
 AN 1994:392567 BIOSIS  
 DN PREV199497405567  
 TI Axonal transport of herpes simplex virions to epidermal cells: Evidence for a specialized mode of virus transport and assembly.  
 AU **Penfold, Mark E. T.**; Armati, Patricia; Cunningham, Anthony L.  
 [Reprint author]  
 CS Virol. Dep., Inst., Clinical Pathol. Med. Research, Westmead Hosp., Westmead 2145 New South Wales, Australia  
 SO Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 14, pp. 6529-6533.  
 CODEN: PNASA6. ISSN: 0027-8424.  
 DT Article  
 LA English  
 ED Entered STN: 14 Sep 1994  
 Last Updated on STN: 14 Sep 1994

AB To examine the transmission of herpes simplex virus (HSV) from axon to epidermal cell, an in vitro model was constructed consisting of human fetal dorsal root ganglia cultured in the central chamber of a dual-chamber tissue culture system separated from autologous skin explants in an exterior chamber by concentric steel cylinders adhering to the substratum through silicon grease and agarose. Axons grew through the agarose viral diffusion barrier and terminated on epidermal cells in the exterior chamber. After inoculation of HSV onto dorsal root ganglia, anterograde axonal transport of glycoprotein and nucleocapsid antigen was observed by confocal microscopy to appear in exterior chamber axons within 12 h and in epidermal cells within 16 h, moving at 2-3 mm/h. Although both enveloped and unenveloped nucleocapsids were observed in the neuronal

soma by transmission electron microscopy, only nucleocapsids were observed in the axons, closely associated with microtubules. Nodule formation at the surface of HSV-infected axons, becoming more dense at the axon terminus on epidermal cells, and patches of axolemmal HSV glycoprotein D expression were observed by scanning (immuno)electron microscopy, probably representing virus emerging from the axolemma. These findings strongly suggest a specialized mode of viral transport, assembly, and egress in sensory neurons: microtubule-associated intermediate-fast anterograde axonal transport of unenveloped nucleocapsids with separate transport of glycoproteins to the distal regions of the axon and assembly prior to virus emergence at the axon terminus.

- CC Cytology - Human 02508  
 Nervous system - Pathology 20506  
 Routes of immunization, infection and therapy 22100  
 Virology - Animal host viruses 33506  
 Medical and clinical microbiology - Virology 36006
- IT Major Concepts  
 Cell Biology; Infection; Microbiology; Neurology (Human Medicine, Medical Sciences)
- IT Miscellaneous Descriptors  
 VIRAL TRANSMISSION
- ORGN Classifier  
**Herpesviridae 03115**  
 Super Taxa  
 dsDNA Viruses; Viruses; Microorganisms  
 Organism Name  
 Herpesviridae  
 Taxa Notes  
 Double-Stranded DNA Viruses, Microorganisms, Viruses
- ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates
- L45 ANSWER 16 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
 AN 1993:334301 BIOSIS  
 DN PREV199345029026  
 TI Molecular cloning, functional expression, and signalling characteristics of a C-C "chemokine" receptor.  
 AU Neote, Kuldeep; Digregorio, David; Mak, John Y.; Horuk, Richard;  
**Schall, Thomas J.**  
 CS Genetech Inc., S. San Francisco, CA 94080, USA  
 SO Journal of Immunology, (1993) Vol. 150, No. 8 PART 2, pp. 204A.  
 Meeting Info.: Joint Meeting of the American Association of Immunologists and the Clinical Immunology Society. Denver, Colorado, USA. May 21-25, 1993.  
 CODEN: JOIMA3. ISSN: 0022-1767.
- DT Conference; (Meeting)  
 LA English  
 ED Entered STN: 16 Jul 1993  
 Last Updated on STN: 17 Jul 1993
- CC General biology - Symposia, transactions and proceedings 00520  
 Genetics - Human 03508  
 Biochemistry studies - Proteins, peptides and amino acids 10064  
 Biochemistry studies - Minerals 10069  
 Biophysics - Molecular properties and macromolecules 10506  
 Biophysics - Membrane phenomena 10508  
 Movement 12100  
 Metabolism - General metabolism and metabolic pathways 13002



Metabolism - Proteins, peptides and amino acids 13012  
 Virology - Animal host viruses 33506  
 Immunology - Bacterial, viral and fungal 34504  
 Immunology - Immunopathology, tissue immunology 34508  
 Medical and clinical microbiology - Virology 36006

IT Major Concepts  
 Biochemistry and Molecular Biophysics; Clinical Endocrinology (Human  
 Medicine, Medical Sciences); Genetics; Immune System (Chemical  
 Coordination and Homeostasis); Infection; Membranes (Cell Biology);  
 Metabolism; Microbiology

IT Chemicals & Biochemicals  
 CALCIUM

IT Miscellaneous Descriptors  
 ABSTRACT; CALCIUM FLUX; CHEMOKINE BINDING AFFINITY;  
 CYTOMEGALOVIRUS INFECTION; LIGAND SPECIFICITY;  
 SEVEN-TRANSMEMBRANE-SPANNING RECEPTOR C-C CKR-1

ORGN Classifier  
 Herpesviridae 03115  
 Super Taxa  
 dsDNA Viruses; Viruses; Microorganisms  
 Organism Name  
 Herpesviridae  
 Taxa Notes  
 Double-Stranded DNA Viruses, Microorganisms, Viruses

ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 7440-70-2 (CALCIUM)

=> => fil wpix

FILE 'WPIX' ENTERED AT 09:09:04 ON 30 JAN 2004  
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FILE LAST UPDATED: 28 JAN 2004 <20040128/UP>  
 MOST RECENT DERWENT UPDATE: 200407 <200407/DW>  
 DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS <<<

>>> SLART (Simultaneous Left and Right Truncation) is now  
 available in the /ABEX field. An additional search field  
 /BIX is also provided which comprises both /BI and /ABEX <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
 PLEASE VISIT:  
[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
 GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM  
 DERWENT UPDATE 200403.  
 THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.  
 SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.  
 FOR FURTHER DETAILS: <http://thomsonderwent.com/chem/polymers/> <<<

=> d all abeq tech abex tot 171

L71 ANSWER 1 OF 2 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN 2002-674849 [72] WPIX  
 DNC C2002-190054  
 TI Collection of **cytomegalovirus** or **cytomegalovirus**  
 infected cells involves contacting a compound that binds  
**cytomegalovirus** or **cytomegalovirus** infected cell with  
 patient's blood.  
 DC B02 B03 B04 D16  
 IN **PENFOLD, M E T; SCHALL, T J**  
 PA (CHEM-N) **CHEMOCENTRYX INC**  
 CYC 100  
 PI WO 2002062956 A2 20020815 (200272)\* EN 41p C12N000-00  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
 NL OA PT SD SE SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM  
 ZW  
 US 2002182594 A1 20021205 (200301) C12Q001-70 <--  
 ADT WO 2002062956 A2 **WO 2002-US3229 20020201**; US 2002182594 A1  
**Provisional US 2001-266094P 20010202**, US 2002-61944 20020201  
 PRAI **US 2001-266094P 20010202**; US 2002-61944 20020201  
 IC ICM C12N000-00; C12Q001-70  
 ICS G01N033-53  
 AB WO 200262956 A UPAB: 20021108  
 NOVELTY - Collection (M1) of **cytomegalovirus (CMV)** or  
**CMV** infected cells from a patient by either inserting a support  
 comprising a compound (A), which binds **CMV** or **CMV**  
 infected cells, into the patient's blood system; or contacting the  
 patient's blood or a tissue containing **CMV** or **CMV**  
 infected cells with (A), so that **CMV** or a **CMV** infected  
 cell in the blood is collected by (A), is new.  
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the  
 following:  
 (1) an apparatus comprising a collector having (A) and a circuit for  
 connecting the blood system of a patient and for flowing the withdrawn  
 blood through it and is in fluid communication with the collector; and  
 (2) assessing mutations in **CMV** involving:  
 (a) collecting **CMV** and/or at least one **CMV**  
 infected cell from a patient by contacting the blood or a tissue of the  
 patient with (A) so that **CMV** or at least one **CMV**  
 infected cell is bound from the blood or tissue; and  
 (b) detecting the presence and/or absence of a mutation in  
**CMV** obtained from the **CMV** or at least one **CMV**  
 infected cell collected in step (2a).  
 ACTIVITY - Virucide.  
 No biological data given.  
 MECHANISM OF ACTION - None given.  
 USE - M1 is useful for collection of **CMV**, or a **CMV**  
 infected cell from humans, animals (claimed) (e.g. monkey, ape, gorilla  
 and baboon, and commercial livestock (e.g. chicken, pig, sheep and cow);  
 for tracking the dissemination or infection of the host; as an in vivo or  
 ex vivo collection mechanism to measure mutation rates and selective

pressures after in vivo passage; and to remove a virus or recombinant virus from a host (e.g. for therapeutic purposes).

ADVANTAGE - The compound expresses on the surface of both virions and infected cells and is involved in viral dissemination by binding to various chemokines.

Dwg.0/1

FS

CPI

FA

AB; GI; DCN

MC

CPI: B04-B04D5; B04-F02; **B04-F11**; B06-B02; B07-D03; B07-D05;  
B07-D06; B11-B; B11-C04A; B11-C08E5; B12-K04A3; B12-K04F; B12-M02D;  
B14-A02A3; **D05-H06**; D05-H10; D05-H13

TECH

UPTX: 20021108

TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred Apparatus: The circuit comprises an outlet line and a return line, each in fluid communication with the blood system of the patient, and the circuit is adapted for withdrawal of the blood from the patient's blood system via the outlet line, passage of the blood through the collector and the return of the blood to the blood system via the return line. The compound is contained on a support within the collector. The support is selected from beads, microspheres, nanoparticles, or colloidal particles. The apparatus further comprises a pump for pumping blood through the circuit. Preferred Device: The support is an implant device for inserting into a patient to contact with the blood of the patient. The implant comprises an absorptive material (preferably a surgical sponge) and is selected from gelfoam, polyester or polyurethane. The support is a patch for applying to the skin.

Preferred Method: Collection of the **CMV** by inserting a support further involves removing the implant device from the patient after **CMV** and/or **CMV** infected cells has accumulated at the implant device. Collection of the **CMV** by contacting the patient's blood or a tissue with compound further involves withdrawing blood containing **CMV** or the **CMV** infected cell from the patient and flowing the blood through or into the collector; and re-circulating the blood back into the patient after the contacting step. The withdrawing, contacting and recirculating steps are performed continuously. The method further involves providing a collection apparatus, the collection apparatus comprising the collector and the circuit; withdrawing the blood from the patient via outlet line and flowing withdrawn blood through the collector; and re-circulating the blood back to the patient via the return line. The method of assessing mutation involves placing an implant device that contains the compound in or on the patient such that the implant device is contacted with the blood of the patient, in which **CMV** or the at least one **CMV** or the one **CMV** infected cell in the blood is captured by (A) of the implant device. If a mutation is detected, the method further involves determining whether the mutation confers resistance to a pharmaceutical agent. The method further involves administering the pharmaceutical compound to the patient prior to the collection step by placing a transdermal patch containing (A) on the skin of the patient.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - The compound is a ligand for **CMV** US28. The compound is of formula  $\text{Ar-C(O)-NR}_{11}\text{-CH}_2\text{-Nhet}$  (I) or its salt (preferably of formula (Ia), (Ib) or (Ic)).  
Ar = substituted aryl group;  
R<sub>11</sub> and R<sub>15</sub> = H or optionally substituted 1-4C alkyl;  
Nhet = optionally substituted 4- to 7-membered nitrogen heterocycle;  
n and m = 1 - 3;  
R<sub>12</sub> - R<sub>14</sub> = R<sub>1</sub> or OH;  
X<sub>1</sub> - X<sub>4</sub> = N or CR<sub>1</sub>;  
R<sub>1</sub> - R<sub>3</sub> = H, halo, 1-4C alkyl, 1-4C alkoxy, 1-4C haloalkyl, 1-4C haloalkoxy, nitro, cyano, 1-4C acyl, amino, 1-4C alkylamino, or di(1-4C)alkylamino;

Y1 - Y4 = N or CR2;  
 Z1 = divalent moiety of (1-3C)alkylene;  
 Z2 = divalent moiety selected from -O-, -S- and -N(R3)-;  
 R'3 = 1-4C alkyl, 1-4C haloalkyl or 1-4C acyl.

L71 ANSWER 2 OF 2 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-269444 [31] WPIX

CR 2002-304220 [34]; 2002-351718 [38]

DNC C2002-080027

TI Assay for identifying a compound useful for blocking **cytomegalovirus** dissemination in a host involves determining whether the compound inhibits binding of a chemokine to US28 or its fragment.

DC B02 B03 B04 D16 K08 S03

IN DAIRAGHI, D J; MCMASTER, B E; SCHALL, T J

PA (CHEM-N) CHEMOCENTRYX INC

CYC 97

PI WO 2002017900 A2 20020307 (200231)\* EN 28p A61K031-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
 NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO  
 RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001087043 A 20020313 (200249) A61K031-00

US 2002127544 A1 20020912 (200262) C12Q001-70

ADT WO 2002017900 A2 WO 2001-US27363 20010830; AU 2001087043 A AU 2001-87043  
 20010830; US 2002127544 A1 Provisional US 2000-228974P 20000830,  
 Provisional US 2000-229191P 20000830, Provisional US 2000-229365P  
 20000830, US 2001-944163 20010830

FDT AU 2001087043 A Based on WO 2002017900

PRAI US 2000-228974P 20000830; US 2000-229191P 20000830; US 2000-229365P  
 20000830; US 2001-944163 20010830

IC ICM A61K031-00; C12Q001-70

ICS A61K031-473; A61K031-498; A61K031-519

AB WO 200217900 A UPAB: 20021001

NOVELTY - An assay for identifying a compound (a), useful for blocking **cytomegalovirus (CMV)** involves determining whether (a) inhibits the binding of a chemokine to US28 or a US28 fragment.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) preventing dissemination of **cytomegalovirus (CMV)** involving administering (a) to block the binding of the chemokine to the US28 or its fragment;  
 (2) reducing cell motility in a **CMV**-infected cell involving contacting the cell with (a) on the surface of the infected cell; and  
 (3) a pharmaceutical composition comprising a compound of formula (I) and a carrier.

X1 - X4 = N or C-R1;

R1 = T;

T = H or T1;

T1 = halogen, 1-4C (halo)alkyl, 1-4C (halo)alkoxy, nitro, cyano, 1-4C acyl, amino, 1-4C alkylamino or di(1-4C alkyl)amino;

Y1 - Y4 = N or C-R2 (preferably CH);

R2 = T;

Z1 = a divalent moiety selected from 1-3C alkylene;

Z2 = a divalent moiety selected from -O-, -S- or -N(R3);

R3 = T; and

R = optionally substituted 4 - 7 membered nitrogen heterocycle.

ACTIVITY - Antiviral; Cardiant; Antiinflammatory; Neuroprotective; Vasotropic.

MECHANISM OF ACTION - Chemokine-US28 receptor or a US28 fragment binding inhibitor; **CMV** dissemination blocker. US28 expressing cells consisted of a mouse cell line stably expressing transfected US28

cDNA under the control of **CMV** promoter were cultured in IMDM-5% FBS and harvested at the concentration of 0.5 - 1 multiply 10 to power 6 cells/ml. The cells were centrifuged and resuspended in assay butter (20 mM HEPES, 140 mM sodium chloride, 1 mM calcium chloride, 5 mM magnesium chloride and with 0.2% bovine serum albumin) to a concentration of 5.6 multiply 10 to power 6 cells/ml. First cells (0.09 ml) was added to 8-assay plates containing **methiothepin** mesylate (a) (having a final concentration of 5 micro g/ml). 125I-Fractalkine (0.09 ml) diluted in assay butter was added, the plates sealed and incubated for 3 hours. The assay plates were harvested, presoaked in PEI solution. Scintillation fluid (35 micro l) was added to all wells, the plates were sealed and counted. Control wells containing diluent or excess fractalkine were used to calculate % of total inhibition for (a). The IC50 of (a) against fractalkine binding on US28-NSO cell was 0.3 micro M.

USE - For identifying compounds useful for blocking **CMV** dissemination in a host (preferably human); which are used for preventing the dissemination of **CMV** in a human; and reducing cell motility in a **CMV**-infected cell (claimed), particularly for treating immuno-compromized individuals such as AIDS patients, neonates or having transplant implantation; in acute and re-immersing infections such as in retinitis, encephalitis, pneumocystis and in other pathologies; and in a variety of inflammatory conditions including coronary artery occlusion following heart transplantation, artherectomy and restenosis following angioplasty.

ADVANTAGE - The compounds prevent the dissemination of **CMV** and reduce cell motility in a **CMV**-infected cell. By inhibiting the dissemination of the virus from the sites of primary or recurrent infection, the compounds can limit the viral spread to secondary organs and thus limit viral replication. Unlike current herpes antiviral agents, the compounds do not act at the stage of viral DNA replication and hence are less prone to problems with toxicity and the development of viral resistance.

Dwg.0/2

FS CPI EPI

FA AB; GI; DCN

MC CPI: B06-H; B11-C10; B14-A02B1; B14-C03; B14-F01; B14-N16

TECH UPTX: 20020516

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (a) is a compound of formula (I) (preferably a compound of formula (Ib)).

m = 0 - 3 (preferably 0);

n = 0 - 3 (preferably 1);

R1' = T1;

R2' = T1 (preferably halogen, 1-4C (halo)alkyl, 1-4C alkoxy or 1-4C alkylthio, especially halogen or 1-4C alkylthio); and

R3' = a substituent selected from 1-4C (halo)alkyl or 1-4C acyl.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The chemokine is fractalkine, MIP-1alpha, -1beta, MCP-1 or RANTES (preferably fractalkine). Preferred Method: The method involves specifically binding labeled fractalkine to the ligand binding domain of US28.

ABEX UPTX: 20020516

SPECIFIC COMPOUNDS - **Methiothepin** and **octoclothePIN** are specifically claimed as (a).

ADMINISTRATION - The compounds are administered parenterally (e.g. intramuscularly or subcutaneously), orally (e.g. sublingually) or rectally. The dosage for parenteral administration is (0.01 - 250, preferably 0.5 - 30, more preferably 1 - 20, especially 1 - 10) mg/kg/day. The dosage for oral administration is (0.5 - 20, preferably 0.05 - 2, especially 0.05 - 0.2) mg/kg/day.

EXAMPLE - No relevant example given.

DEFINITIONS - Preferred Definitions:  
 X1, X3 and X4 and Y1 - Y4 = CH; and  
 R = substituted 6-membered heterocycle.

=> d all abeq tech abex tot 172

L72 ANSWER 1 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN 2003-851613 [79] WPIX  
 CR 2003-332863 [31]; 2003-342441 [32]; 2003-662906 [62]  
 DNC C2003-239899  
 TI Composition useful for treating **cytomegalovirus** or  
**cytomegalovirus**-related diseases e.g. atherosclerosis comprises  
 arylamine derivatives and a carrier.  
 DC B03 B05  
 IN DAIRAGHI, D J; MCMASTER, B E; PENFOLD, M; SCHALL, T J;  
 WRIGHT, J J  
 PA (CHEM-N) **CHEMOCENTRYX INC**  
 CYC 1  
 PI US 2003114423 A1 20030619 (200379)\* 18p A61K031-675  
 ADT US 2003114423 A1 Provisional US 2001-316386P 20010830, US 2002-233336  
 20020829  
 PRAI US 2001-316386P 20010830; US 2002-233336 20020829  
 IC ICM A61K031-675  
 ICS A61K031-4178; A61K031-454; A61K031-4709; A61K031-496; A61K031-5377  
 AB US2003114423 A UPAB: 20031208  
 NOVELTY - A pharmaceutical composition (C1) comprises arylamine  
 derivatives and a carrier.  
 DETAILED DESCRIPTION - A pharmaceutical composition comprises  
 arylamine of formula Ar-L-N(R1)-R2 (I) and a carrier.  
 Ar = 5 - 14 membered heteroaryl group or 6-14C aryl (both optionally  
 substituted);  
 q = 0 - 3;  
 R5 = halo, NO2, CN, R, OR, NR2, CO2R, C(O)R, OC(O)R, NRC(O)R or  
 NRC(O)NR2;  
 R = H or 1-8C alkyl;  
 R3 and R4 = 1-4C alkyl;  
 L = linkage having 2 - 14 contiguous chain atoms selected from C, N,  
 O, P and S (optionally mono- - tetra-substituted by T1);  
 R1 and R2 = 1-4C alkyl (optionally mono- - tetra-substituted by T1);  
 T1 = halo, OR', SR', S(O)pR' or CO2R';  
 R' = H or R3;  
 p = 1 or 2;  
 N(R1R2) and N(R3R4) = a ring selected from aziridine, azetidine,  
 pyrrolidine, piperidine, imidazoline, piperazine or morpholine (all  
 optionally mono- - tri-substituted by T2); and  
 T2 = 1-4C alkyl, phenyl, phenyl(1-4C)alkyl, hydroxy,  
 hydroxy(1-4C)alkyl, 1-4C alkoxy(1-4C)alkyl or di(1-4C)alkylamino(1-  
 4C)alkyl.  
 An INDEPENDENT CLAIM is included for arylamine of formula (Ia).  
 m and n = 1 or 2;  
 R'1 and R'2 = 1-4C alkyl (optionally substituted by OH or 1-4C  
 alkoxy);  
 N(R'1R'2) = N(R1R2);  
 R'3 and R'4 = R3; and  
 N(R'3R'4) = Q1;  
 Q1 = aziridine, azetidine, pyrrolidine or piperidine (optionally  
 mono- or di-substituted by 1-4C alkyl).  
 ACTIVITY - Virucide; Antiarteriosclerotic; Cardiovascular-Gen.  
 MECHANISM OF ACTION - Inhibitor of chemokine (preferably fractalkine,  
 RANTES, MCP-3, MIP-1 alpha and MCP-1) binding to US28;  
**cytomegalovirus (CMV)** dissemination blocker.  
 CMV dissemination inhibiting activity of

1-diethylamino-3-(5-nitro-2-pyrrolidin-1-yl-phenoxy)-propan-2-ol (A) was determined by an assay providing an indication of fractalkine binding to US28. Human foreskin fibroblast (HFF) cell lines were transfected with US28cDNA. The cells were cultured in a buffer (containing IMDM-5% FBS), centrifuged and re-suspended in assay buffer. Aliquots of the cells were then contacted with (A) and labeled with fibroblasts. The assay mixture was incubated for 2 - 4 hours at 4 deg. C. Following the incubation the assay wells were harvested under vacuum, plates were sealed and the wells were counted. IC50 was determined which was less than 1 micro M.

USE - For treating **CMV** or **CMV**-related diseases (claimed) e.g. atherosclerosis or cardiovascular disease; to treat disease or provide medical prophylaxis to individuals who possess a compromised immune system or suffer immunosuppressed conditions e.g. prior to undergoing immunosuppressive therapy in connection with organ transplantation or anticancer chemotherapy.

ADVANTAGE - (I) inhibits chemokine binding to US28 on the surface of an infected cell or virion.

Dwg.0/0

FS

CPI

FA

AB; GI; DCN

MC

CPI: B06-D01; B06-D02; B06-D03; B06-D05; B07-D01; B07-D03; B07-D05;  
B14-A02; B14-F01; B14-F02; B14-F07; B14-G02

ABEX

UPTX: 20031208

ADMINISTRATION - (C1) is administered in a daily dosage of 2 - 2000 mg orally, parenterally (including intramuscularly, intravenously or subcutaneously) or topically. The oral dosage is 0.05 - 20 (preferably 0.05 - 2, especially 0.05 - 0.2) mg/kg of body weight per day. The parenteral dosage is 0.01 - 250 (preferably 0.5 - 30, especially 1 - 20) mg/kg/day.

EXAMPLE - No relevant example given.

DEFINITIONS - Preferred Definitions:

Ar = N(R3)(R4)-phenyl (substituted by (R5)q);

R1, R2, R'1 and R'2 = ethyl;

L = -NH-CH(CH3)CH2CH2CH2-, -CH2CH2-, -OCH2CH(OH)CH2- or -NHCH2CH2CH2-;

R5 = halo, NO2, CN, CO2R or C(O)R;

R = H or 1-4C alkyl;

N(R3R4) = pyrrolidine, piperidine or morpholine;

m and n = 1; and

N(R'3R'4) = a pyrrolidine ring.

L72 ANSWER 2 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-662906 [62] WPIX

CR 2003-332863 [31]; 2003-342441 [32]

DNC C2003-180024

TI Treatment of **cytomegalovirus** or its related diseases e.g. retinitis and encephalitis, involves use of bicyclic compounds..

DC B02

IN DAIRAGHI, D J; MCMASTER, B E; PENFOLD, M; SCHALL, T J;  
WRIGHT, J J

PA (CHEM-N) **CHEMOCENTRYX**

CYC 1

PI US 2003149055 A1 20030807 (200362)\* 29p A61K031-506

ADT US 2003149055 A1 Provisional US 2001-316386P 20010830, US 2002-233326  
20020829

PRAI US 2001-316386P 20010830; US 2002-233326 20020829

IC ICM A61K031-506

ICS A61K031-4439; A61K031-46; A61K031-4709

AB US2003149055 A UPAB: 20030928

NOVELTY - Treatment of **cytomegalovirus** or its related diseases involves administration of bicyclic compounds (I).

DETAILED DESCRIPTION - Treatment of **cytomegalovirus** or its related diseases involves administration of bicyclic compounds of formula

Ar-C(R2)(OR1)-Z (I).

Ar = optionally substituted 5-14 membered heteroaryl group having 1-5 heteroatoms;

R1 = optionally substituted (hetero)aryl(1-4C alkyl), -C(O)R11 or C(O)NR11R12;

R11 and R12 = (hetero)aryl, (hetero)aryl(1-4C alkyl), 4-8C cycloalkyl(1-4C alkyl) or hetero(4-8C cycloalkyl)(1-4C alkyl) (all optionally substituted);

R2 = H or 1-8C alkyl; and

Z = optionally substituted hetero(6-10C bicycloalkyl).

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Virucide; Ophthalmological; Neuroprotective; Antiinflammatory; Respiratory; Cardiant; Vasotropic.

MECHANISM OF ACTION - US28-Receptor-Binding-Chemokine-Inhibitor.

The efficacy of 3-nitro-benzoic acid quinolin-4-yl-(5-vinyl-1-azabicyclo(2.2.2)oct-2-yl)-methyl ester (A) to inhibit binding of fractalkine to US28 receptor was evaluated by radioligand binding assay. The target cells - US68 transfected murine cells (4 multiply 10<sup>5</sup> - 5 multiply 10<sup>6</sup> cells/ml) (0.09 ml) were added to assay plates containing (A) (0.02 ml) diluted in dimethylsulfoxide. 125I-fractalkine ( approx. 50 micro M) was added to the assay plate and the plates were sealed. After incubation at 4 deg. C for 2-4 hours, the plates were harvested on a Packard vacuum cell harvester. Scintillation fluid was added to the wells, the plates were sealed and then counted in a Top count scintillation counter. (A) showed an IC<sub>50</sub> value of less than 1 micro M.

USE - For inhibiting chemokine (e.g. fractalkine) to US28 on the surface of an infected cell or virion; for treating **cytomegalovirus** or its related diseases (claimed) (e.g. retinitis, encephalitis, pneumocystis, coronary artery occlusion following heart transplant and atherectomy, and restenosis following angioplasty).

ADVANTAGE - The bicyclic compounds are potent inhibitors of US28 receptor.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B07-H; B14-F01; B14-F02; B14-L06; B14-N03; B14-N16

TECH UPTX: 20030928

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compound: The bicyclic compound is also of formula (Ia).

n = 0 - 3;

R13 = halo, NO<sub>2</sub>, CN, R, OR, NR<sub>2</sub>, CO<sub>2</sub>R, C(O)R, OC(O)R, NRC(O)R or NRC(O)NR<sub>2</sub>;

R = H or 1-8C alkyl;

R14 = H or optionally substituted 1-8C alkyl (preferably unsaturated 2-8C alkyl, particularly vinyl).

ABEX UPTX: 20030928

SPECIFIC COMPOUNDS - 7 Compounds are specifically claimed as (I), e.g. 3-nitro-benzoic acid quinolin-4-yl-(5-vinyl-1-azabicyclo(2.2.2)oct-2-yl)-methyl ester (Ib).

ADMINISTRATION - The dosage is 2-2000 mg/day. The dosage for oral administration is 0.05-20 (preferably 0.05-2, especially 0.05-0.2) mg/kg/day, and for parenteral (e.g. intramuscular, intravenous, or subcutaneous) administration is 0.01-250 (preferably 1-100, especially 0.5-30, particularly 1-20) mg/kg/day. Administration is also rectally, topically or by intraocular implant.

EXAMPLE - No relevant example given.

DEFINITIONS - Preferred Definitions:

Ar = quinoline, isoquinoline, pyridine or pyrimidine;

R1 = C(O)R11 or C(O)NR11R12;



R2 = H; and

Z = 1-azabicyclo(2.2.2)octane, 2-azabicyclo(2.2.2)octane, 1-azabicyclo(3.2.2)nonane, 2-azabicyclo(3.2.2)nonane, 1-azabicyclo(2.2.1)heptane or 2-azabicyclo(2.2.1)heptane.

L72 ANSWER 3 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-342441 [32] WPIX

CR 2003-332863 [31]; 2003-662906 [62]; 2003-851613 [79]

DNC C2003-089814

TI Treatment of **cytomegalovirus** infections or related diseases, using O-substituted 1-heteroaryl-1-heterobicycloalkyl-alkanol compounds, preferably cinchonidine benzoate derivatives.

DC B02

IN DAIRAGHI, D J; MCMASTER, B E; PENFOLD, M; SCHALL, T J; WRIGHT, J J

PA (CHEM-N) CHEMOCENTRYX INC

CYC 101

PI WO 2003018549 A2 20030306 (200332)\* EN 38p C07D000-00

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM GR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT WO 2003018549 A2 WO 2002-US28007 20020829

PRAI US 2001-316386P 20010830

IC ICM C07D000-00

AB WO2003018549 A UPAB: 20031208

NOVELTY - Treatment of **cytomegalovirus** (CMV) diseases or CMV-related diseases involves administration of an O-substituted 1-heteroaryl-1-heterobicycloalkyl-alkanol derivative (I).

DETAILED DESCRIPTION - Treatment of CMV diseases or CMV-related diseases involves administration of a heterobicyclic compound of formula (I).

Ar = optionally substituted (os) 5-14 membered heteroaryl;

R1 = os aryl-(1-4C) alkyl, heteroaryl-(1-4C) alkyl, COR11 or

CONR11R12;

R11, R12 = os aryl, os aryl-(1-4C) alkyl, aryl-(1-4C) alkyl, os (4-8C) cycloalkyl-(1-4C) alkyl, os heteroaryl, os heteroaryl-(1-4C) alkyl or os (4-8C) heterocycloalkyl-(1-4C) alkyl;

R2 = H or 1-8C alkyl;

Z' = os 6-10C heterobicycloalkyl.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising a compound (I) and a carrier.

ACTIVITY - Virucide; Ophthalmological; Neuroprotective; Antiinflammatory; Antiarteriosclerotic; Cardiant. 2-Chlorobenzoic acid cinchonidine ester (Ia) had an IC50 less than 1 micro M against rhesus CMV.

MECHANISM OF ACTION - Inhibition of chemokine binding to US28 on infected cell or virion surface.

(Ia) had an IC50 1-10 micro M for inhibition of hUS28 binding.

USE - (I) inhibit the binding of chemokines (especially fractalkine) to US28 on the surface of infected cells or virions (claimed), and are thus useful for inhibiting viral dissemination during acute or re-emerging CMV infection. (I) are typically used for the treatment of CMV infections in immunocompromized patients (e.g. AIDS patients, neonates or patients undergoing immunosuppressive therapy in connection with organ transplantation or anticancer chemotherapy); or for treating CMV-related diseases (e.g. retinitis, encephalitis, pneumocystitis, atherosclerosis or cardiovascular disease) in non-immunocompromized patients.

ADVANTAGE - (I) are small molecule inhibitors of the CMV

US28 receptor.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B04-A02; B07-H; B14-A02; B14-L06

TECH UPTX: 20030522

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (I) are cinchonine (or analog) benzoate ester derivatives of formula (I').

n = 0-3;

R13 = halo, NO<sub>2</sub>, CN, R, OR, N(R)<sub>2</sub>, COOR, OCOR, NRCOR or NRCON(R)<sub>2</sub>;

R = H or 1-8C alkyl;

R14 = H or os 1-8C alkyl (preferably unsaturated 2-8C alkyl, especially vinyl).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (I) are typically prepared by reaction of an aldehyde or ketone of formula ArCOR<sub>2</sub> with a Grignard reagent of formula Z'-Mg-Br, followed by O-alkylation or O-acylation of the obtained alcohol.

ABEX UPTX: 20030522

SPECIFIC COMPOUNDS - 7 Compounds (I) are specified in the claims, e.g. 2-chlorobenzoic acid cinchonidine ester (Ia).

ADMINISTRATION - Administration is oral, parenteral or topical at a daily dose of 2-2000 mg, preferably 0.05-20, especially 0.05-0.2 mg/kg/day orally. (I) are optionally used in combination with other drugs, such as other antiviral agents (e.g. ganciclovir), anti-HIV agents (e.g. AZT) or immunosuppressants (e.g. cyclosporin).

DEFINITIONS - Preferred Definitions:

Ar = quinoline, isoquinoline, pyridine or pyrimidine;

Z' = 1- or 2-azabicyclo (2.2.2)-octane, 1- or 2-azabicyclo (3.2.2)-nonane or 1- or 2-azabicyclo (2.2.1)-octane;

R1 = COR11 or CONR11R12;

R2 = H.

L72 ANSWER 4 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-332863 [31] WPIX

CR 2003-342441 [32]; 2003-662906 [62]; 2003-851613 [79]

DNC C2003-086287

TI Treatment of **cytomegalovirus** or related diseases comprising administration of arylamines.

DC B03 B05

IN DAIRAGHI, D J; MCMASTER, B E; PENFOLD, M; SCHALL, T J;

WRIGHT, J J

PA (CHEM-N) **CHEMOCENTRYX INC**

CYC 101

PI WO 2003020029 A1 WO 20030313 (200331)\* EN 39p A01N033-02

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU  
MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA  
ZM ZW

ADT WO 2003020029 A1 WO 2002-US27812 20020829

PRAI US 2001-316386P 20010830

IC ICM A01N033-02

ICS A01N031-14; A01N033-18; A01N033-24; A61K031-075; A61K031-135

AB WO2003020029 A UPAB: 20031208

NOVELTY - **Cytomegalovirus (CMV)** or **CMV**

-related diseases are treated by administering arylamines (I).

DETAILED DESCRIPTION - **Cytomegalovirus (CMV)** or

**CMV**-related diseases are treated by administering arylamines of formula Ar-L-N-R1R2 (I).

Ar = 5 - 14 membered heteroaryl or 6-14C aryl (both optionally substituted);

L = optionally substituted 2 - 14 contiguous chain atom containing C, N, O, P or S (optionally substituted by T1);

R1, R2 = 1-4C alkyl (optionally substituted by T1); or

NR1R2 = aziridine, azetidine, pyrrolidine, piperidine, imidazoline, piperazine or morpholine (all optionally mono- to tri-substituted by 1-4C alkyl, phenyl, phenyl(1-4C)alkyl, OH, hydroxy(1-4C)alkyl, 1-4C alkoxy(1-4C)alkyl or di(1-4C)alkylamino(1-4C)alkyl;

T1 = halo, OR', SR', S(O)PR' or CO2R';

R' = H or 1-4C alkyl; and

p = 1 or 2.

An INDEPENDENT CLAIM is also included for an arylamine of formula (Ia).

m, n = 1 or 2;

R6, R7 = 1-4C alkyl (optionally substituted by OH or 1-4C alkoxy); or NR6R7 = NR1R2; and

R3, R4 = 1-4C alkyl; or

NR3R4 = aziridine, azetidine, pyrrolidine or piperidine (optionally mono- - di-substituted by 1-4C alkyl).

ACTIVITY - Virucide.

MECHANISM OF ACTION - Chemokine Binding Inhibitor.

In radioligand binding assays on rhesus dermal fibroblast cells (4 multiply 105 - 5 multiply 106) infected with **cytomegalovirus** (CMV) (I) was found to have an IC50 value of less than 1 micro M for binding of labeled fractalkine to the US28 surface receptor.

USE - (I) Are used for treating **cytomegalovirus** (CMV) or CMV related diseases (claimed) such as atherosclerosis or cardiovascular diseases. They are useful for patients with a compromised immune system or those who are expected to suffer immunosuppressed condition (such as those about to undergo immunosuppressive therapy in connection with organ transplant or anticancer chemotherapy). They inhibit chemokine (particularly fractalkine) binding to US28 on the surface of infected cells or virions.

ADVANTAGE - (I) Are in the form of pro-drug which can be metabolically or chemically converted into the active drug by the recipient host, which rely on hydrolytic cleavage or oxidative activation of the pro-drug. The composition containing (I) can be combined with other pharmaceutical agents like antiviral agents and these compositions show high efficacy.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-B01E; B05-B01F; B07-H; B10-B02A; B10-B02B; B10-B04B; B14-A02; B14-A02A3; B14-F02; B14-F07; B14-G01; B14-G02; B14-G02C; B14-G03; B14-L01

ABEX UPTX: 20030516

SPECIFIC COMPOUNDS - 1 Compound (I) is specifically disclosed, i.e.

(S)-1-((2-pyrrolidino-5-nitro)phenoxy)-3-(N,N-diethylamino)propan-2-ol (Ib).

ADMINISTRATION - The dosage is 2 - 2000 mg/kg and is administered rectally, topically, intraocularly, or parenterally (including intramuscularly, intravenously or subcutaneously). The dosage for oral administration is 0.05 - 20 (preferably 0.05 - 0.2) mg/kg.

EXAMPLE - N-(2-hydroxy-4-nitrophenyl)pyrrolidine (3 g), (S)-(+)-epichlorohydrin (1.4 g) and dry potassium carbonate (2.6 g) in dry acetonitrile (40 ml) were stirred at 60 degrees C overnight. Water (100 ml) was added and the mixture was worked up to give a crude epoxide (3 g, 78%).

The crude epoxide (100 mg) and diethylamine (3 ml) were stirred at room temperature overnight. The solution was concentrated, and the yellow product was purified by column chromatography (eluant was 0.2% methanol in

chloroform) to give (S)-1-((2-pyrrolidino-5-nitro)phenyloxy)-3-(N,N-diethylamino)propan-2-ol (60 mg, 47%).

# DEFINITIONS - Preferred Definitions:

Ar = phenyl (substituted by NR3R4 and optionally mono- - tri-substituted by R5);

L = -NHCH(CH3)CH2CH2CH2-, -CH2CH2-, -OCH2CH(OH)CH2- or -NHCH2CH2CH2-;

R1, R2, R6, R7 = ethyl;

R5 = halo, NO2, CN, CO2R or C(O)R;

R = H or 1-4C alkyl; and

NR3R4 = pyrrolidine, piperidine or morpholine.

L72 ANSWER 5 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-643385 [69] WPIX

DNC C2004-014231

TI Recombinant **cytomegalovirus** with a **CMV** genome with a first heterologous nucleotide sequence encoding a heterologous chemokine element, useful for inducing an immune response, and in therapeutic or prophylactic treatments.

DC B04 C06 D16

IN **PENFOLD, M E T; SCHALL, T J**

PA (CHEM-N) **CHEMOCENTRYX INC**

CYC 101

PI WO 2002062296 A2 20020815 (200269)\* EN 74p A61K000-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM  
ZW

US 2002176870 A1 20021128 (200281) A61K039-245

EP 1364037 A2 20031126 (200380) EN C12N015-83

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI TR

ADT WO 2002062296 A2 WO 2002-US3228 20020201; US 2002176870 A1 Provisional US  
2001-265925P 20010202, US 2002-61943 20020201; EP 1364037 A2 EP  
2002-707692 20020201, WO 2002-US3228 20020201

FDT EP 1364037 A2 Based on WO 2002062296

PRAI US 2001-265925P 20010202; US 2002-61943 20020201

IC ICM A61K000-00; A61K039-245; C12N015-83

ICS A61K039-25; C12N007-00

AB WO 200262296 A UPAB: 20040115

NOVELTY - A new recombinant **cytomegalovirus (CMV)** (I) comprising a **CMV** genome with a first heterologous nucleotide sequence encoding a heterologous chemokine element, and a second heterologous nucleotide sequence encoding an immunogenic polypeptide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a recombinant **CMV** comprising a genome with a heterologous nucleotide sequence encoding a heterologous chemokine or ligand, or an immunogenic polypeptide;

(2) inducing (M1) an immune response in a host comprising administering a composition of (I);

(3) therapeutic or prophylactic treatment (M2) comprising administering a composition of (I) to an animal, where the immunogenic polypeptide comprises an antigen correlated with a disease or infection which the animal has or is susceptible to obtaining, and where the administration induces an immune response in the animal; and

(4) preparing (M3) (I).

ACTIVITY - Virucide.

No suitable data given.

MECHANISM OF ACTION - Gene therapy; Vaccine.

USE - (I) are useful for inducing an immune response in a host and in treatment methods, either therapeutically or prophylactically (claimed).

Dwg.0/8

FS CPI

FA AB; DCN

MC CPI: B04-B04C; B04-E03F; **B04-F11**; B14-A02; B14-G01; B14-S03;  
B14-S11; C04-B04C; C04-E03F; **C04-F11**; C14-A02; C14-G01;  
C14-S03; C14-S11; **D05-H06A**; D05-H12A

TECH UPTX: 20030513

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred **Cytomegalovirus**:

The **CMV** genome in (I) is encapsulated in infectious form as a virion, and attenuated to reduce virulency in a host. The viral dissemination gene is disabled, and is a gene encoding a viral chemokine element or a viral immune-modulatory gene. The gene encoding the viral chemokine element is selected from US28, US27, UL33, UL78, UL146, UL147, MCK-1 and MCK-2, or their homolog. The viral immune-modulatory gene is selected from UL111A, US3, US6, US11, US2, UL83, UL18, UL40, m144, m152, m04, m06 and m138, or their homolog. The host is selected from a non-human primate or commercial livestock. The mammal is a rhesus monkey or a mouse. The heterologous chemokine element is endogenous to the host, and is a chemokine ligand or receptor. The **CMV** genome is attenuated to reduce virulency in a mammal and the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog. The immunogenic polypeptide comprises an antigen from a pathogenic organism or a tumor antigen. The pathogenic organism is a bacterium, a virus or a parasite. The immunogenic polypeptide further comprises a fragment of a polypeptide from organisms selected from *Bacillus anthracis*, Dengue, *Yersinia pestis*, Ebola, Marburg, Lassa, Venezuelan Equine Encephalitis or Eastern Equine Encephalitis. The immunogenic polypeptide preferably comprises a tumor antigen, and is selected from antigens associated with breast cancers, lung cancers, thyroid carcinomas, squamous cell carcinomas or renal cell carcinomas. The first and second heterologous nucleotide sequence are operably linked to a or different promoters that is operative in the host. The construct is formulated as a composition, the composition comprising the construct and an adjuvant, carrier, diluent or excipient. (I) further comprises:

- (a) the immunogenic polypeptide comprising an antigen from an organism that is pathogenic in humans or a human tumor antigen;
- (b) a viral chemokine element or a viral immune-modulatory gene is disabled, the viral chemokine element selected from US28, U827, UL33, UL78, UL146 and UL147 and the viral immune-modulatory gene selected from UL111A, US3, US6, US11, US2, UL83, UL18 and UL40; and
- (c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog.

The **CMV** genome in the recombinant virus is attenuated by virtue of a disabled viral dissemination gene and/or a viral immune-modulatory gene, and is attenuated to reduce virulency in a host and encapsulated in infectious form. The immunogenic polypeptide comprises an antigen from an organism that is pathogenic in a host or a tumor antigen.

Preferred Method: The **CMV** genome in (M1) is attenuated to reduce virulency in the host, and is disabled. The viral dissemination gene is a gene encoding a viral chemokine element or a viral immune-modulatory gene. The gene encoding the viral chemokine element is selected from US28, US27, UL33, UL78, UL146, UL147, MCK-1 and MCK-2, or their homolog. The viral immune-modulatory gene is selected from UL111A, US3, US6, US11, US2, UL83, UL18, UL40, m144, m152, m04, m06 and m138, or a homolog. The heterologous chemokine element is endogenous to the host. The heterologous chemokine element is a chemokine ligand or receptor. The host is a mammal and the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog. The pathogenic organism is a bacterium, a virus or a parasite. (M1) further comprises:

- (a) the host is a human;
- (b) a viral chemokine element or a viral immune-modulatory gene is

disabled, the viral chemokine element selected from US28, US27, UL33, UL78, UL146, and UL147 and the viral immune-modulatory gene selected from UL111A, US3, US6, US11, US2, UL83, UL18 and UL40;

(c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog; and

(d) the immunogenic polypeptide comprises an antigen from an organism that is pathogenic in humans or a human tumor antigen.

The method alternatively comprises:

(a) the host is a rhesus monkey;

(b) a viral chemokine element or a viral immune-modulatory gene is disabled, the viral chemokine element selected from rhUS28.1, rhUS28.2, rhUS28.3, rhUS28.4, rhUS28.5, rhUL33 and rhUL78 and the viral immune-modulatory gene selected from rhUL111A, US3, US6, US11, US2, UL83 and UL40;

(c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog; and

(d) the immunogenic polypeptide comprises an antigen from a pathogenic organism or a tumor antigen.

The method further comprises:

(a) the host is a mouse;

(b) a viral chemokine element or a viral immune-modulatory gene is disabled, the viral chemokine element selected from MUL78, MCK-1 and MCK-2 and the viral immune-modulatory gene selected from m144, m152, m04, m06, m138;

(c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC, CCR7 or their homolog;

(d) the immunogenic polypeptide comprises an antigen from a pathogenic organism or a tumor antigen.

The CMV genome in (M2) is attenuated by virtue of a disabled viral dissemination gene. The viral dissemination gene is a gene encoding a viral chemokine element or a viral immune-modulatory gene. The gene encoding the viral chemokine element is selected from US28, US27, UL33, UL78, UL146, UL147, MCK-1 and MCK-2, or their homolog. The viral immune-modulatory gene is selected from UL111A, US3, US6, US11, US2, UL83, UL18, UL40, m144, m152, m04, m06 and m138, or a homolog. The animal is a mammal. The animal is selected from a human, a non-human primate and commercial livestock. The mammal is from a non-human primate and a mouse.

The method further comprises:

(a) the host is a human;

(b) a viral chemokine element or a viral immune-modulatory gene is disabled, the viral chemokine element selected from US28, US27, UL33, UL78, UL146, and UL147 and the viral immune-modulatory gene selected from UL111A, US3, US6, US11, US2, UL83, UL18 and UL40;

(c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog; and

(d) the immunogenic polypeptide comprises an antigen from an organism that is pathogenic in humans or a human tumor antigen.

The method alternatively comprises:

(a) the host is a rhesus monkey;

(b) a viral chemokine element or a viral immune-modulatory gene is disabled, the viral chemokine element selected from rhUS28.1, rhUS28.2, rhUS28.3, rhUS28.4, rhUS28.5, rhUL33 and rhUL78 and the viral immune-modulatory gene selected from rhUL111A, US3, US6, US11, US2, UL83 and UL40;

(c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog; and

(d) the immunogenic polypeptide comprises an antigen from a pathogenic organism or a tumor antigen.

The method further comprises:

(a) the host is a mouse;

(b) a viral chemokine element or a viral immune-modulatory gene is disabled, the viral chemokine element selected from MUL78, MCK-1 and MCK-2 and the viral immune-modulatory gene selected from m144, m152, m04, m06,

m138;

(c) the heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC, CCR7 or their homolog;

(d) the immunogenic polypeptide comprises an antigen from a pathogenic organism or a tumor antigen.

(M3) further comprises attenuating the **CMV** genome to reduce virulency in a host. The attenuation comprises disabling a viral dissemination gene. The viral dissemination gene is a gene encoding a viral chemokine element or a viral immune-modulatory gene. The gene encoding the viral chemokine element is selected from US28, US27, UL33, UL78, UL146, UL147, MCK-1 and MCK-2, or their homolog. The viral immune-modulatory gene is selected from UL111A, US3, US6, US11, US2, UL83, UL18, UL40, m144, m152, m04, m06 and m138, or their homolog. The host is selected from a human, a non-human primate and commercial livestock. The mammal is selected from the group consisting of a rhesus monkey and a mouse. The heterologous chemokine element is endogenous to the host, and is a chemokine ligand or receptor. The heterologous chemokine element is selected from MIP3alpha, SLC, MDC, MC10, MIP1beta, ELC and CCR7, or their homolog. The immunogenic polypeptide comprises an antigen from a pathogenic organism or a tumor antigen. The pathogenic organism is a bacterium, a virus or a parasite. The method further comprises inserting at least one promoter that is operative in the host into the **CMV** genome such that the at least one promoter is operably linked to the first and second heterologous nucleotide sequence. The method alternatively comprises inserting at least two promoters that are operative in the host into the **CMV** genome such that the first and second heterologous nucleotide sequence are operably linked to different promoters. The method further comprises combining (I) with a carrier, diluent or excipient.

ABEX UPTX: 20030513

ADMINISTRATION - The vaccine preparations dose are from 10 to 107 pfu per dose, preferably 103-106. Routes of administration include intradermal, subcutaneous, oral, intramuscular, intraperitoneal and transdermal.

EXAMPLE - Experimental protocols are described but no results are given.

L72 ANSWER 6 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-426421 [45] WPIX

DNC C2002-120897

TI Inhibiting proliferation of peripheral blood mononuclear cells and reducing cytokine production of monocytes using rhesus or human **cytomegalovirus** interleukin-10, for treating e.g. immune disorders.

DC B04

IN PENFOLD, M; SCHALL, T J; SPENCER, J; PENFORD, M

PA (CHEM-N) CHEMOCENTRIX INC

CYC 97

PI WO 2002032457 A1 20020425 (200245)\* EN 69p A61K045-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU  
SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001080911 A 20020429 (200255) A61K045-00

US 2002197234 A1 20021226 (200304) A61K038-20

EP 1307228 A1 20030507 (200332) EN A61K045-00

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI TR

ADT WO 2002032457 A1 WO 2001-US23942 20010730; AU 2001080911 A AU 2001-80911  
20010730; US 2002197234 A1 Provisional US 2000-221831P 20000728, US  
2001-919224 20010730; EP 1307228 A1 EP 2001-959344 20010730, WO  
2001-US23942 20010730

FDT AU 2001080911 A Based on WO 2002032457; EP 1307228 A1 Based on WO

2002032457

PRAI US 2000-221831P 20000728; US 2001-919224 20010730

IC ICM A61K038-20; A61K045-00

ICS A01N037-18; A61K038-28; A61K039-12; C07K001-00; C12N005-08

AB WO 200232457 A UPAB: 20020717

NOVELTY - Inhibition of proliferation of peripheral blood mononuclear cells (PBMCs) and reduction of cytokine production of monocytes involves contacting the cells in vitro with rhesus or human **cytomegalovirus** interleukin (**CMV** IL)-10.

ACTIVITY - Immunosuppressive; Antiinflammatory; Vasotropic; Antipsoriatic; Ophthalmological; Dermatological; Neuroprotective; Antirheumatic; Antiarthritic; Antiulcer; Antithyroid; Thyromimetic; Antidiabetic; Antiallergic; Asthmatic; Virucide; Hepatotropic; Respiratory-Gen.; Cytostatic; and Antibacterial.

MECHANISM OF ACTION - PBMCs proliferation and cytokine production inhibitor.

USE - For inhibiting the proliferation of PBMCs and reducing the cytokine production of monocytes, for preventing or treating immune disorders (preferably in kidney transplant patients) (e.g. graft versus host disease, autoimmune disease, inflammatory response (preferably chronic inflammatory response e.g. rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Grave's disease, Hashimoto's thyroiditis, scleroderma, insulin-dependent diabetes mellitus, allergic response and asthma), pathologic delayed type hypersensitivity response, endotoxin-induced toxic shock (toxic shock syndrome), granulomatous disease, psoriasis, uveitis, systemic lupus erythematosus, multiple sclerosis, contact-dermatitis, leukemia and type TH1 immune response to transplanted graft of organs (e.g. cornea, lung, heart, liver, bone marrow, kidney, pancreas, blood, and skin)), respiratory viral infection, for ameliorating symptoms of hepatitis, for ameliorating liver damage, liver disease or liver fibrosis and for reducing an in vivo inflammatory response with substantially elevated levels of interleukin (IL)-1 alpha, GM-CSF, IFN- gamma or (TNF)- alpha (all claimed). Also for treating cytokine-mediated diseases including endotoxin-induced septic shock (bacterial septic shock), cell mediated cytotoxicity immune disorders, hypersensitivity immune disorders, chronic immune disorders, graft rejection and cancer.

ADVANTAGE - The treatment of monocytes with **CMV** IL-10 reduces cytokine production, monocyte surface expression of classical class I major histocompatibility complex (MHC) and class II MHC molecules and increases monocyte surface expression of the nonclassical class I MHC molecule, HLA-G which is beneficial in the treatment of various diseases. Dwg.0/12

FS CPI

FA AB; DCN

MC CPI: B04-H02L; B14-A02; B14-C03; B14-C06; B14-E08; B14-E10C; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-K01A; B14-N03; B14-N11; B14-N12; B14-N17; B14-N17C; B14-S01; B14-S04; B14-S06

TECH UPTX: 20020717

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method further involves adding an agent that induces the PBMCs to proliferate. The levels of interferon (IFN)-gamma and tumor necrosis factor- (TNF)-alpha secreted by the PBMCs and the monocytes and the levels of GM-CSF, IL-1alpha and IL-6 secreted by the monocytes are reduced in response to the contacting step. The proliferation level, the secretion of IFN-gamma, TNF-alpha, GM-CSF, IL-1alpha or IL-6 and the cytokine levels are monitored to determine a reduction in their levels.

Preferred Materials: The rhesus or human **CMV** IL-10 is a component of a composition further comprising a carrier. The composition is sterile, substantially isotonic and prepared under GMP conditions.

ABEX UPTX: 20020717

ADMINISTRATION - The dosage of purified human **CMV** IL-10 is 100 ng/ml, 1 ng/ml, 10 pg/ml, 100 pg/ml, 1 pg/ml or 100 ng/ml - 1 pg/ml.



Administration is oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, intratracheal, intravenous, intramuscular, subcutaneous, or by inhalation in a local or systemic manner or in a depot or sustained release formulation.

EXAMPLE - Peripheral blood mononuclear cells (PBMCs) from nine human donors were tested for effects on proliferation in the presence of rhesus **cytomegalovirus** interleukin (CMV IL)-10, recombinant hIL-10 (1 mug/ml) conditioned media or mock conditioned media and PBMC proliferation was measured by using (3H)TdR incorporation assays. The % inhibition was 57 - 91%. Human PBMC proliferation for four donors inhibited in the presence of hIL-10 (1 mug/ml) was 16 - 81% while four other donors showed enhanced proliferation of 24 - 194% and one donor showed modest enhancement. The mean % change in proliferation with CMV IL-10 and IL-10 was -50 to -100 and 0 - 50 respectively. The experiment was also conducted similarly with human CMV IL-10 and IL-10 with almost the same results for the % change in proliferation.

L72 ANSWER 7 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN 2002-351718 [38] WPIX  
 CR 2002-269444 [31]; 2002-304220 [34]  
 DNN N2002-276368 DNC C2002-099891  
 TI Isolated or recombinant homologs of US28 proteins and nucleic acids encoding the proteins, for use in vaccine compositions for treating an animal infected with, or at risk of infection by, **cytomegalovirus**  
 DC B02 B03 B04 D16 K08 S03  
 IN DAIRAGHI, D J; MCMASTER, B E; SCHALL, T J; PENFOLD, M E  
 T; PENFOLD, M  
 PA (CHEM-N) CHEMOCENTRIX INC; (PENF-I) PENFOLD M E T; (SCHA-I) SCHALL T J  
 CYC 98  
 PI WO 2002018954 A2 20020307 (200238)\* EN 95p G01N033-569  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
 NL OA PT SD SE SL SZ TR TZ UG ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO  
 RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
 AU 2001088682 A 20020313 (200249) G01N033-569  
 US 2002127544 A1 20020912 (200262) C12Q001-70  
 US 2003175681 A1 20030918 (200362) C12Q001-70  
 EP 1350113 A2 20031008 (200370) EN G01N033-569  
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
 RO SE SI TR  
 ADT WO 2002018954 A2 WO 2001-US27392 20010830; AU 2001088682 A AU 2001-88682  
 20010830; US 2002127544 A1 Provisional US 2000-228974P 20000830,  
 Provisional US 2000-229191P 20000830, Provisional US 2000-229365P  
 20000830, US 2001-944163 20010830; US 2003175681 A1 Provisional US  
 2000-229365P 20000830, US 2001-944049 20010830; EP 1350113 A2 EP  
 2001-968433 20010830, WO 2001-US27392 20010830  
 FDT AU 2001088682 A Based on WO 2002018954; EP 1350113 A2 Based on WO  
 2002018954  
 PRAI US 2000-229365P 20000830; US 2000-228974P 20000830; US 2000-229191P  
 20000830; US 2001-944163 20010830; US 2001-944049 20010830  
 IC ICM C12Q001-70; G01N033-569  
 ICS A61K031-473; A61K031-498; A61K031-519; A61K039-245; A61K039-255;  
 A61K039-265; A61K039-27; A61K039-395; A61K048-00; A61P031-12;  
 C07K014-00; C12N005-00; C12N015-00; C12P019-34; C12P021-06  
 AB WO 200218954 A UPAB: 20031030  
 NOVELTY - An isolated or recombinant homolog of US28 protein (I) which  
 binds a chemokine (encoded by an open reading frame in the unique short  
 (US) region in human **cytomegalovirus** (CMV) genome),

having at least 75% identity to a sequence (S1) fully defined in the specification, over a region of at least 40 amino acids in length, or a protein comprising at least 12 amino acids of S1, is new.

DETAILED DESCRIPTION - S1 comprises a sequence of 344, 339, 340, 328, 485, 401, 365 or 423 amino acids fully defined in the specification (amino acid sequences of rhesus monkey proteins RhUS28.1, RhUS28.2, RhUS28.3, RhUS28.4, RhUS28.5, RhUL78 (encoded by an open reading frame 78 in the unique long (UL) region of **CMV** genome), RhUL33 and RhUL33 spliced, respectively).

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated, purified or recombinant nucleic acid (II) encoding (I) (US28 homolog);

(2) a vector comprising (II);

(3) a cell comprising (II);

(4) a vaccine (III) comprising an immunogenic **CMV** polypeptide encoded by at least a region of **CMV** genome in which the polynucleotide sequence encoding US28 or its homolog has been inactivated;

(5) identifying (M1) an agent that reduces **CMV** dissemination in an animal, by determining whether the agent (A) inhibits the expression or activity of US28 or US28 homolog, or fragment or variant of US28 or US28 homolog; and

(6) treating (M2) an animal infected with **CMV** or at risk of infection by **CMV**, by administering (A) to the animal.

ACTIVITY - Virucide; neuroprotective; antiinflammatory; ophthalmological.

MECHANISM OF ACTION - Inhibitor of **CMV** dissemination; inhibitor of binding of chemokine to US28; vaccine (claimed).

No suitable data given.

USE - (III) is useful for treating an animal infected with **cytomegalovirus** or at a risk of infection by **CMV**. (III) is also useful for inducing a therapeutic or protective immune response in a patient and in methods for treating diseases including retinitis, encephalitis and pneumocystis caused by **CMV** infection.

Dwg.0/7

FS CPI EPI

FA AB; DCN

MC CPI: B04-B04B1; B04-B04D5; B04-B04G; B04-C01G; B04-E02F; B04-E03F; B04-E05; B04-E06; B04-E07; B04-E08; B04-F0100E; B04-G08; B04-N02A; B04-N02A0E; B11-C07A; B11-C08E5; B11-C09; B12-K04A4; B14-A02A3; B14-C03; B14-N03; B14-N16; B14-S11A; **D05-H06A**; D05-H07; D05-H12A; D05-H12D1; D05-H12D2; D05-H12D4; D05-H12E; D05-H14B2; D05-H17A6; D05-H18B

EPI: S03-E14H; S03-E14H4

TECH UPTX: 20020618

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is produced by standard recombinant techniques.

Preferred Method: M1 involves contacting a chemokine with US28, US28 homolog, its fragment or variant, or a cell expressing the above said compounds, in the presence of (A) and determining whether (A) inhibits the binding between the chemokine and US28, its homolog, fragment or variant. The (A) is an antibody that specifically binds to (I), or a small molecule. The cell is infected with **CMV** or transfected with a heterologous nucleic acid encoding US28, its homolog, fragment or variant. The protein comprises at least 10 contiguous amino acids of S1 and binds to the chemokine. The method further involves administering (A) to a non-human animal infected with **CMV** and determining whether (A) inhibits the dissemination of **CMV** from a primary site of infection in non-human animal such as primate e.g. rhesus monkey. The **CMV** is rhCMV. The method further involves determining whether viral titer in a saliva, urine or blood sample obtained from the non-human animal is detectably less than viral titer in a corresponding sample obtained from a control animal. The method further involves obtaining a

peripheral blood sample from a non-human animal, amplifying a region of **CMV** which is present in the sample with a set of primers that specifically hybridize to a set of **CMV** genome to form an amplified product, and detecting the amplified product. The method involves obtaining and staining a tissue sample of a non-human animal with an antibody that specifically binds to **CMV**. Alternately, activated T cells and/or memory cells in a peripheral blood sample taken from the non-human animal are detected. In M2, (A) interferes with the expression of a target nucleic acid encoding (I) in cells of the animal. The interference is achieved by administering an antisense nucleic acid that specifically hybridizes to a target nucleic acid or ribozyme that specifically recognizes the target nucleic acid. The target nucleic acid encodes US28, human UL33 or human UL78. The (A) is a vaccine which generates an immune response in an animal, where the vaccine is attenuated through inhibition of expression or activity of US28 or US28 homolog. The vaccine comprises an immunogenic human **cytomegalovirus** (HCMV) polypeptide encoded by at least a region of hCMV genome in which the polynucleotide segment US28 or UL33 or UL78 has been inactivated. The **CMV** titer is reduced by 5-fold or greater as measured in blood, saliva or urine, following administration of (A). The interference results in a delay in appearance or reduction of levels of reactive leucocyte in the peripheral blood of the animal.

Preferred Sequence: (I) is encoded by a nucleic acid segment that hybridizes under stringent conditions to a sequence comprising 1085, 990, 1019, 991, 1460, 1150, 996 or 1339 nucleotides fully defined in the specification. The immunogenic **CMV** polypeptide in (III) is an HCMV polypeptide encoded by at least a region of the HCMV genome.

ABEX

UPTX: 20020618

WIDER DISCLOSURE - Disclosed are pharmaceutical compositions for prophylactically or therapeutically treating **CMV** infections.

SPECIFIC SEQUENCES - (I) comprises a sequence of 344, 339, 340, 328, 485, 401 or 423 amino acids fully defined in the specification, and are encoded by a sequence comprising 1085, 990, 1019, 991, 1460, 1150, 996 or 1339 nucleotides fully defined in the specification (claimed).

ADMINISTRATION - (III) is administered through oral, intranasal, intraperitoneal, intravenous, intramuscular, subcutaneous, subdermal or transdermal route. The dosage is 0.05-20 mg/kg, preferably 1-10 mg/kg/day.

EXAMPLE - Rhesus dermal fibroblasts (RhDF) were infected with rhesus **cytomegalovirus** (**CMV**) strain 68.1. At 96 hours post infection supernatants were collected, and virions were pelleted. The isolated virions were resuspended in TE buffer and proteinase K added to a final concentration of 0.2 microg/ml, sodium dodecyl sulfate to a final concentration of 1% and RnaseA to a final concentration of 10 microg/ml. The resulting mixture was incubated for 2 hours at 65degreesC. Viral DNA was precipitated with ethanol and then subjected to sequencing. The DNA was used to create a shot gun library using hydroshearing and producing inserts of about 3000 nucleotides in length. Individual clones were sequenced using ABI Prism BigDye terminator chemistry. The 220 kb genome was covered to an average accuracy of 6x sequence. Individual reads were assembled into contiguous fragments. Homologs of human **CMV** genes were elucidated using the basic local alignment search tool X program. Sequence was further analyzed using the BioNavigator bio-informatic program set. Analysis of the rhCMV genome indicated the presence of a number of open reading frames having homology with the human **CMV** US28 open reading frame. The regions of homology were referred to as rhUS28.1 (comprising 344 nucleotides), rhUS28.2 (comprising 339 nucleotides), rhUS28.3 (comprising 340 nucleotides), rhUS28.4 (comprising 328 nucleotides) and rhUS28.5 (comprising 485 nucleotides). Other regions having homology to human UL33 and human UL78 were also identified and named rhUL33 (comprising 401 nucleotides), rhUL33 spliced (comprising 365 nucleotides) and rhUL78 (comprising 423 nucleotides) (sequences fully

defined in the specification).

L72 ANSWER 8 OF 8 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN 2002-304220 [34] WPIX  
 CR 2002-269444 [31]; 2002-351718 [38]  
 DNC C2002-088487  
 TI Diagnosis of **cytomegalovirus** useful for treating  
**cytomegalovirus** infection involves the use of a detectable and a  
 labeled amount of an image generating non-endogenous substituted aromatic  
 compound.  
 DC B02 B03 B04 D16 K08 S03  
 IN DAIRAGHI, D J; MCMASTER, B E; SCHALL, T J  
 PA (CHEM-N) **CHEMOCENTRYX INC**; (CHEM-N) **CHEMOCENTRYX**  
 CYC 97  
 PI WO 2002017969 A2 20020307 (200234)\* EN 28p A61K051-04  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
 NL OA PT SD SE SL SZ TR TZ UG ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO  
 RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
 AU 2001087007 A 20020313 (200249) A61K051-04  
 US 2002127544 A1 20020912 (200262) C12Q001-70  
 US 2002193374 A1 20021219 (200303) A61K051-00  
 ADT WO 2002017969 A2 WO 2001-US27269 20010830; AU 2001087007 A AU 2001-87007  
 20010830; US 2002127544 A1 Provisional US 2000-228974P 20000830,  
 Provisional US 2000-229191P 20000830, Provisional US 2000-229365P  
 20000830, US 2001-944163 20010830; US 2002193374 A1 Provisional US  
 2000-229191P 20000830, US 2001-944051 20010830  
 FDT AU 2001087007 A Based on WO 2002017969  
 PRAI US 2000-229191P 20000830; US 2000-228974P 20000830; US 2000-229365P  
 20000830; US 2001-944163 20010830; US 2001-944051 20010830  
 IC ICM A61K051-00; A61K051-04; C12Q001-70  
 ICS A61K031-40; A61K031-445; A61K031-473; A61K031-495; A61K031-498;  
 A61K031-519; A61K031-535  
 AB WO 200217969 A UPAB: 20030113  
 NOVELTY - Diagnosis of **cytomegalovirus (CMV)** involves  
 administering an image-generating compound to a subject having **CMV**

DETAILED DESCRIPTION - Diagnosis of **cytomegalovirus (CMV)** involves administering an image generating compound of  
 formula Ar-C(=O)-N(R11)-CH2-A (I) or its salt.

Ar = substituted aryl group;

R11 = H or optionally substituted 1-4C alkyl; and

A = optionally substituted 4-7 membered nitrogen heterocycle.

INDEPENDENT CLAIMS are also included for the followings:

(1) treating **CMV** in a human involving administering a  
 compound, which blocks the binding of a chemokine to US28 or its fragment;  
 and

(2) reducing cell motility in a **CMV**-infected cell involving  
 contacting the cell with a motility-reducing compound that inhibits  
 chemokine binding to US28 on the surface of the cell.

ACTIVITY - Virucide.

MECHANISM OF ACTION - Blocker and inhibitor of chemokine (preferably  
 fractalkine, MIP-1 alpha, MIP-1 beta, MCP-1 or RANTES) binding.

US28 expressing cells consisted of a mouse cell line stably  
 expressing transfected US28 cDNA under the control of **CMV**  
 promoter were cultured in IMDM-5% FBS and harvested at the concentration  
 of 0.5 - 1 multiply 10<sup>6</sup> cells/ml. The cells were centrifuged and  
 resuspended in assay buffer (HEPES (20 mM), sodium chloride (140 mM),  
 calcium chloride (1 mM), magnesium chloride (5 mM) and with bovine serum  
 albumin (0.2%)) to a concentration of 5.6 multiply 10<sup>6</sup> cells/ml. First  
 cells (0.09 ml) was added to 8 assay plates containing

S-(-)-3-iodo-2-hydroxy-6-methoxy-N((1-ethyl-2-pyrrolidinyl)methyl)-benzamide (a) (having a final concentration of 5 micro g/ml). 125I-Fractalkine (0.09 ml) diluted in assay buffer was added, the plates sealed and incubated for 3 hours at 4 deg. C. The assay plates were harvested, pre-soaked in PEI solution. Scintillation fluid (35 micro l) was added to all wells, the plates were sealed and counted. Control wells containing diluent or excess fractalkine were used to calculate % of total inhibition for (a). The IC50 of (a) against fractalkine binding on US28-NSO cell was 0.6 micro M.

USE - For diagnosis of **CMV**, for treating **CMV** in a human and for reducing cell motility in a **CMV**-infected cell (claimed); in PET (undefined), SPET (undefined) and tracer analysis.

ADVANTAGE - The compound inhibits chemokine binding to US28 on the surface of a **CMV**-infected cell or blocks the chemokine binding to US28 or its fragment. The compound provides IC50 value of at most 50 (preferably at most 20, more preferably at most 10, especially less than 1) micro g/ml.

Dwg.0/3

FS CPI EPI

FA AB; GI; DCN

MC CPI: B07-D03; B07-H; B14-A02; B14-L06; K08-X; K09-E

TECH UPTX: 20020528

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compound: The compound is labeled with a radioisotope selected from 18F, 75Br, 123I or 125I.

ABEX UPTX: 20020528

SPECIFIC COMPOUNDS - 3-Iodo-2-hydroxy-6-methoxy-N((1-ethyl-2-pyrrolidinyl)methyl)-benzamide (IBZM) and 123I-IBZM are specifically claimed as (I).

ADMINISTRATION - The compound can be administered orally, topically, rectally or parenterally (including intramuscularly, intravenously or subcutaneously) in a dosage of about 2-2000 mg per day. For oral route, the dosage of (I) is 0.05-20 (preferably 0.05-2, especially 0.05-0.2) mg/kg of body weight per day, and for parenteral administration is 0.01-250 (preferably 1-10, more preferably 0.5-30, especially 1-20) mg/kg/day.

EXAMPLE - No relevant example given.

DEFINITIONS - Preferred Definitions:

Ar = substituted phenyl;

A = pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl or piperidyl (all optionally substituted);

R11 = H;

R12 - R14 = H, -OH, halo, 1-4C alkyl or 1-4C alkoxy;

R15 = 1-4C alkyl.

Preferably (I) is a compound of formula (Ia).

n = 1-3 (preferably 1);

R15 = R11;

R12 - R14 = H, OH, halo, 1-4C (halo)alkyl, 1-4C (halo)alkoxy, nitro, cyano, 1-4C acyl, (1-4C alkyl)amino or di(1-4C)alkylamino.

With the proviso that at least one of R12 - R14 is other than H and that (i) when n is 1, R11 is H, R12 - R14 are H, OH, halo, 1-4C alkyl or 1-4C alkoxy and R15 is 1-4C alkyl or when n is 1, R11 is H, R15 is 1-4C alkyl then R12 - R14 are all other than H.

=> => d his

(FILE 'HOME' ENTERED AT 08:04:17 ON 30 JAN 2004)

DEL HIS

FILE 'REGISTRY' ENTERED AT 08:05:18 ON 30 JAN 2004

L1 STR  
L2 50 S L1  
L3 1769 S L1 FUL  
SAV TEMP L3 LE061/A  
L4 STR L1  
L5 25 S L4 CSS SAM SUB=L3  
L6 561 S L4 CSS FUL SUB=L3  
SAV TEMP L6 LE061A/A  
L7 STR L4  
L8 19 S L7 CSS SAM SUB=L6  
L9 457 S L7 CSS FUL SUB=L6  
SAV TEMP L9 LE061B/A

FILE 'HCAPLUS' ENTERED AT 08:20:19 ON 30 JAN 2004

L10 618 S L9  
L11 13257 S CMV OR ?CYTOMEGALOVIR?  
E CYTOMEGALOVIR/CT  
E E4+ALL  
L12 2971 S E7  
L13 5744 S E6+NT  
E CYTOMEG/CT  
E E6+ALL  
L14 2 S L10 AND L11-L13  
E SCHALL T/AU  
L15 128 S E3-E10  
E PENFOLD M/AU  
L16 17 S E4-E6  
E CHEMOCENTR/PA,CS  
L17 33 S E5-E14  
E CHEMO CENTR/PA,CS  
L18 2 S L10 AND L15-L17  
L19 1 S US20020182594/PN OR (WO2002-US3229 OR US2001-266094#)/AP,PRN  
L20 3 S L14,L18,L19  
L21 3 S L20 AND L10-L20  
SEL HIT RN

FILE 'REGISTRY' ENTERED AT 08:24:11 ON 30 JAN 2004

L22 4 S E1-E4

FILE 'REGISTRY' ENTERED AT 08:24:33 ON 30 JAN 2004

FILE 'MEDLINE' ENTERED AT 08:24:56 ON 30 JAN 2004

L23 356 S L9  
L24 989 S OCTOCLOTHEPIN? OR CLOTEPIN? OR CLOTHEPIN? OR CLOROTHEPIN? OR  
L25 989 S L23,L24  
L26 28347 S L11  
E CYTOMEGALOVIR/CT  
E E6+ALL  
L27 11117 S E9+NT  
E CYTOMEGALOVIR/CT  
E E9+ALL  
L28 14342 S E5+NT  
E CYTOMEGALOVIR/CT  
E E77+ALL  
L29 22 S E10+NT  
E CYTOMEGALOVIRUS/CT  
E E82+ALL  
L30 1546 S E2+NT  
L31 351 S E4+NT  
L32 0 S L25 AND L26-L31  
E SCHALL T/AU  
L33 89 S E3-E7  
E PENFOLD M/AU

L34 12 S E3-E5,E8,E9  
L35 0 S L25 AND L33,L34  
L36 10 S L26-L31 AND L33,L34

FILE 'BIOSIS' ENTERED AT 08:31:11 ON 30 JAN 2004

L37 1228 S L25  
L38 31590 S L11  
L39 82214 S HERPESVIRIDAE+NT/BC  
E 02220/BC  
E 02162/BC  
E CYTOMEGA/BC  
E HERP/BC  
L40 0 S L37 AND L38,L39  
E SCHALL T/AU  
L41 146 S E3-E9  
E PENFOLD M/AU  
L42 13 S E4-E7  
L43 0 S L37 AND L41,L42  
L44 16 S L38,L39 AND L41,L42

FILE 'MEDLINE, BIOSIS' ENTERED AT 08:49:21 ON 30 JAN 2004  
L45 16 DUP REM L36 L44 (10 DUPLICATES REMOVED)

FILE 'REGISTRY' ENTERED AT 08:49:32 ON 30 JAN 2004

FILE 'HCAPLUS' ENTERED AT 08:49:55 ON 30 JAN 2004

FILE 'MEDLINE, BIOSIS' ENTERED AT 08:50:44 ON 30 JAN 2004

FILE 'WPIX' ENTERED AT 08:51:22 ON 30 JAN 2004

L46 3651 S L11/BIX  
L47 61 S C07K014-045/IC,ICM,ICS,ICA,ICI  
L48 328 S C12N015-38/IC,ICM,ICS,ICA,ICI  
L49 1927 S (B04-B02B4 OR C04-B02B4)/MC  
L50 5359 S (B04-F11 OR C04-F11)/MC  
L51 6234 S (D05-H06 OR D05-H06A OR D05-H12F)/MC  
L52 93 S (D430(S)F553)/M0,M1,M2,M3,M4,M5,M6  
L53 20 S L24/BIX  
E OCTOCLOTHEPIN/DCN  
E CLOTEPIN/DCN  
E METITEPIN/DCN  
E METHIOTEPIN/DCN  
L54 0 S L46-L51 AND L52  
L55 1 S L46-L51 AND L53  
E SCHALL T/AU  
L56 29 S E3-E5  
E PENFOLD M/AU  
L57 10 S E3,E4  
E CHEMOCENT/PA  
L58 24 S E4,E5  
L59 10 S L46-L51 AND L56-L58  
L60 1 S L52,L53 AND L56-L58  
L61 10 S L55,L59,L60  
L62 1 S L19  
L63 10 S L62,L61 AND L46-L62  
L64 1 S L55 AND L63  
L65 9 S L63 NOT L64  
L66 325 S (D420(S)F553)/M0,M1,M2,M3,M4,M5,M6  
L67 3 S L66 AND L46-L51  
L68 11 S L67,L63-L65  
L69 1 S L68 NOT L63  
L70 10 S L68 NOT L69  
L71 2 S L70 AND L67

L72 8 S L70 NOT L71

FILE 'WPIX' ENTERED AT 09:09:04 ON 30 JAN 2004

L73 13897 S L46-L51  
L74 1899 S L73 AND C12Q001-70/IC, ICM, ICS  
L75 3256 S L73 AND G01N033-5?/IC, ICM, ICS  
L76 6527 S L73 AND (B12-K04? OR C12-K04?)/MC  
L77 90 S (B06-B02 OR C06-B02)/MC AND (B07-D05 OR C07-D05)/MC  
L78 465 S L77, L52, L53, L66  
L79 3 S L78 AND L73  
L80 1 S L79 NOT L70  
L81 1 S L80, L69

=>